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A STUDY OF THE HEMAGGLUTININ PRODUCED IN RESPONSE TO THE ADMINISTRATION OF P³² TAGGED ERYTHROCYTES

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THE exact mechanisms of antibody production are unknown and lie entirely within the realm of theory. The first attempt at explanation was offered by Buchner,³ who felt that antibody during its formation actually incorporated antigen or fragments of antigen within its own molecular structure. Later theories attempting to explain antibody formation excluded the possibility that antigen formed an integral part of the antibody molecule. Ehrlich⁹ hypothesized that certain body cells possessed preformed "receptors" or side chains capable of uniting with specific antigens, and under stimulation additional receptors could be manufactured and later separated from their cellular attachment entering the circulation. Breinl and Haurowitz,² Alexander,¹ and Mudd²¹ independently advanced theories to the effect that antigen, penetrating to the site of globulin production and coming into direct contact with the newly forming globulin molecule, modifies globulin synthesis by serving as a model or framework about which at least a portion of the antibody globulin molecule takes shape. Pauling's²² elaboration on this idea required that the continued synthesis and presence of antibody is dependent upon the persistence of antigen within the body. Sabin²⁵ believed that antibody formation comes about as the result of the influence of antigens altering the cytoplasm within the macrophage, which is responsible for globulin synthesis. Burnet⁴ has suggested that continued production of antibody or modified globulin occurs as the result of the modification of intracellular enzymes or proteinases responsible for protein destruction and synthesis upon their first contact with antigen.

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MAY-JUNE, 1951

281

Evidence has been presented to disprove the theory that antigen or portions of it are actually incorporated within the antibody molecule. Hooker and Boyd¹⁸ have shown from quantitative data that the disproportion between the large amount of antibody formed in response to the injection of a relatively small quantity of antigen makes this hypothesis mathematically inconsistent. Further support of this has been offered by Heidelberger, Kendall, and Soo Hoo.¹⁶ Hooker and Boyd¹⁹ further showed that when specially prepared arsenic-containing proteins were injected into rabbits, no arsenic could be detected chemically in the antiserum produced in response to these synthetic antigens. Similar findings were reported by Haurowitz, Vardar, and Schwerin,¹⁵ employing such antigens as iodo-proteins, bromo-proteins, and phosphoro-proteins. Jordan²⁰ attempted to revive Buchner's original theory stating that antibodies are formed by the autocatalytic reproduction of antigen molecules and are identical or nearly identical with the antigen containing their determinant group or a related group, should this grouping be foreign, artificial, or incapable of reproduction by the immunized organism.

The problem of whether or not antigen forms an integral portion of the antibody molecule is further considered in this study using a radioactive-tagged antigen. Erythrocytes were labeled with radioactive phosphorus and an attempt made to detect whether any of the radioactive portion was contained in the resultant hemagglutinating antibody.

MATERIALS AND METHODS

P³² tagged erythrocytes of sheep and white leghorn chickens were employed as immunizing antigens. Two ml of packed erythrocytes were placed in a solution containing 5 ml of physiological sodium chloride and 15 ml of phosphate buffer at pH 7. To this was added two millicuries of P³² in the form of phosphoric acid neutralized to pH 7. This red cell suspension was then placed in a water bath at 37°C for one hour, agitated, centrifuged, and the supernatant discarded. The packed red cells were then washed with physiological saline and recentrifuged several times until the supernatant fluid of the final washing showed negligible radioactivity. Aliquot portions of the P³² activated erythrocytes were assayed for radioactivity, and radioautographs were made of these cells.

Albino male rats having an average weight of 275 to 300 gm were immunized with either chicken or sheep erythrocytes. Each animal received 0.5 ml of a 5 per cent suspension of erythrocytes intravenously through the saphenous vein. Ten rats received P³² activated chicken erythrocytes, and five received nonactivated chicken erythrocytes. Ten other rats received activated sheep erythrocytes and five rats, nonactivated sheep cells. At the end of five days, these rats were bled from the heart and the individual sera collected. A hemagglutinin titer was done on each serum as well as radioactivity measurements of the whole serum and the antibody-containing portion.

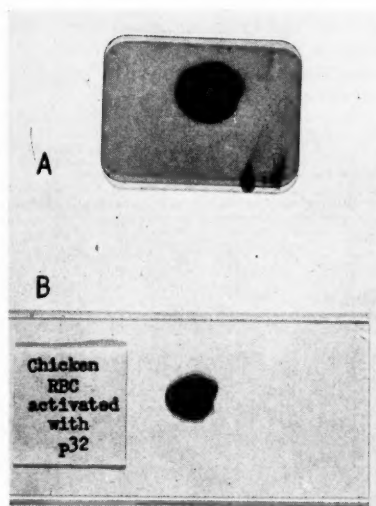


Fig. 1. (A) Radioautograph, on x-ray film of (B) thick smear of P³² tagged chicken erythrocytes.

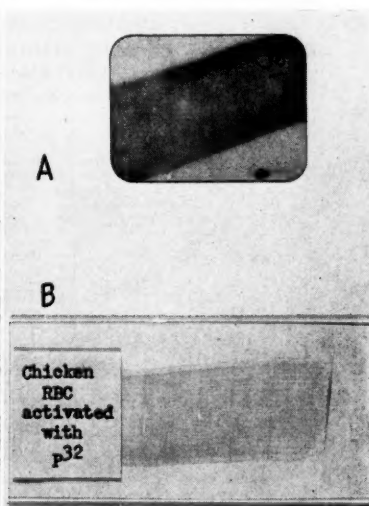


Fig. 2. (A) Radioautograph, on x-ray film of (B) thin smear of P³² tagged chicken erythrocytes.

In the titration of serum hemagglutinins each serum was incubated in a water bath at 57°C. for one half hour to inactivate complement. To each 0.5 ml of ascending serum dilutions was added 0.2 ml of a 4 per cent suspension of normal chicken or sheep erythrocytes, depending on the individual antiserum. The tubes were placed in a water bath at 37°C for one hour. Readings were then made and the tubes placed in a refrigerator over night, at which time readings were again made. The titer of the serum was read as the serum dilution in the last tube showing agglutination of red cells. Controls were run with normal rat serum plus chicken and sheep erythrocytes and antiserum plus canine erythrocytes.

The hemagglutinating antibodies were separated as antigen-antibody complex. The antisera were placed in a water bath at 57°C for one hour to inactivate complement. To 0.5 ml portions of sera were added 0.2 ml of a 4 per cent suspension of normal nonactivated chicken or sheep erythrocytes, depending upon the type of the individual antiserum. The tubes were then incubated in a water bath at 37°C for one hour and placed in a refrigerator overnight. The agglutinated red cell mass was then separated from the supernatant serum and the same procedure repeated several times with this serum until no further agglutination of red cells took place. In this way the maximal amount of hemagglutinating antibody was extracted from the serum. The pooled red cell masses agglutinated by one antiserum (i.e., antigen plus antibody) were assayed for radioactivity, and radioautographs were made.

P³² TAGGED ERYTHROCYTES—COHEN ET AL

TABLE I. COMPARISON OF RADIOACTIVITY MEASUREMENTS OF INTRAVENOUSLY ADMINISTERED P³² ACTIVATED CHICKEN ERYTHROCYTE ANTIGEN, THE RESULTANT ANTISERUM, AND THE ANTIBODY PORTION OF SERUM (AS ANTIGEN-ANTIBODY COMPLEX)

Rat No.	Radioactivity of Injected Erythrocytes (0.5/cc-5%)	Radioactivity of Rat Antiserum 5 Days Later Counts/min./ml*	Hemagglutinin Titer of Serum	Radioactivity of Normal Erythrocytes Agglutinated by Antisera Counts/min./gm*	Radioactivity of Agglutinated RBC Mass (Antigen-Antibody Complex)	
					Counts/min./gm*	Radioautograph
1	4 x 10 ⁷ **	4.37	1:2000	0	0	Neg.
2	4 x 10 ⁷	12.6	1:6400	0	0	Neg.
3	4 x 10 ⁷	3.2	1:3200	0	0	Neg.
4	4 x 10 ⁷	2.3	1:2000	0	0	Neg.
5	4 x 10 ⁷	9.8	1:1600	0	0	Neg.
6	4 x 10 ⁷	7.3	1:1600	0	0	Neg.
7	4 x 10 ⁷	18.15	1:1600	0	0	Neg.
8	8 x 10 ⁶ ***	0	1:6400	0	0	Neg.
9	8 x 10 ⁶	0	1:6400	0	0	Neg.
10	8 x 10 ⁶	0	1:6400	0	0	Neg.
11	0	0	1:3200	0	0	Neg.
12	0	0	1:3200	0	0	Neg.
13	0	0	1:1600	0	0	Neg.
14	0	0	1:6400	0	0	Neg.
15	0	0	1:6400	0	0	Neg.

*All counts shown above represent actual counts from which background counts were subtracted.

**16 x 10⁶ counts/min./gm of erythrocytes.

***3.2 x 10⁶ counts/min./gm of erythrocytes.

In assaying P³² erythrocytes, antiserum, and the agglutinated red cell masses (antigen-antibody complex) for radioactivity, an aliquot portion of each was placed in a planchet, ashed, and counted under a thin window (1.4 mg/cm²) Geiger tube coupled to an autoscaler. The activity was arbitrarily recorded in counts per minute per unit weight. Radioautographs were prepared in the following manner: a thin coat of liquid plastic glaze was painted on the surface of a glass slide. On the surface of this was placed a smear of activated erythrocytes, antisera, or the agglutinated red cell mass. After a few minutes, when this material had dried, it was covered with a sheet of thin cellophane. In a darkroom a dental size x-ray film was placed over the cellophane, and this in turn was covered with a glass slide. The glass slides, held together with a rubber band, were then placed between sheets of black paper and left in the darkroom for periods of one to three weeks. After this period of exposure the x-ray films were developed in the usual manner.

RESULTS

Tables I and II summarize our findings. Assays on the activated erythrocyte antigens show that these cellular antigens carried a significant degree of radioactivity. Radioautographs made from smears of these cells (Figs.

P³² TAGGED ERYTHROCYTES—COHEN ET AL

TABLE II. COMPARISON OF RADIOACTIVITY MEASUREMENTS OF INTRAVENOUSLY ADMINISTERED P³² ACTIVATED SHEEP ERYTHROCYTE ANTIGENS, THE RESULTANT ANTISERUM, AND THE ANTIBODY PORTION OF SERUM (AS ANTIGEN-ANTIBODY COMPLEX)

Rat No.	Radioactivity of Injected Erythrocytes (0.5/cc-5%)	Radioactivity of Rat Antiserum 5 Days Later Counts/min./ml*	Hemagglutinin Titer of Serum	Radioactivity of Normal Erythrocytes Agglutinated by Antisera Counts/min./gm*	Radioactivity of Agglutinated RBC Mass (Antigen-Antibody Complex)	
					Counts/min./gm*	Radioautograph
16	10.5 x 10 ⁵ **	2.7	1:3200	0	0	Neg.
17	10.5 x 10 ⁵	0.9	1:3200	0	0	Neg.
18	10.5 x 10 ⁵	0	1:1600	0	0	Neg.
19	10.5 x 10 ⁵	3.18	1:3200	0	0	Neg.
20	10.5 x 10 ⁵	0	1:3200	0	0	Neg.
21	10.5 x 10 ⁵	0	1:1600	0	0	Neg.
22	10.5 x 10 ⁵	0.21	1:3200	0	0	Neg.
23	10.5 x 10 ⁵	0	1:3200	0	0	Neg.
24	10.5 x 10 ⁵	0	1:1600	0	0	Neg.
25	10.5 x 10 ⁵	0	1:1600	0	0	Neg.
26	0	0	1:1600	0	0	Neg.
27	0	0	1:3200	0	0	Neg.
28	0	0	1:1600	0		Neg.
29	0	0	1:3200	0	0	Neg.
30	0	0	1:1600	0	0	Neg.

*All counts shown above represent actual counts from which background counts were subtracted.

**4.02 x 10⁶ counts/min./gm erythrocytes.

3 and 4) indicate that the activity was within the cells and not in the fluid medium. This was corroborated by obtaining negligible counts from the supernatant saline used to wash these cells following the activation.

Hemagglutinin titrations of the rat antiserum five days following administration of the antigen indicates a satisfactory degree of antibody production by these animals in response to the administration of radioactive antigen.

Normal nonactivated species specific erythrocytes were added to the antiserum in order to separate the antibody portion. Satisfactory agglutination of the red cells by the hemagglutinating antibody followed. Repetitions of this procedure resulted in the maximal removal of hemagglutinins from the sera. Assay of the antigen-antibody complex revealed no discernible activity. Radioautographs made from these agglutinated cell masses were likewise negative, indicating the absence of radioactivity within the antibody portion of the serum.

In seven of the animals that had received radioactive chicken erythrocytes there was a very small degree of radioactivity found in the antiserum that measured from 2.3 to 18.15 counts per minute per cc. Four of the

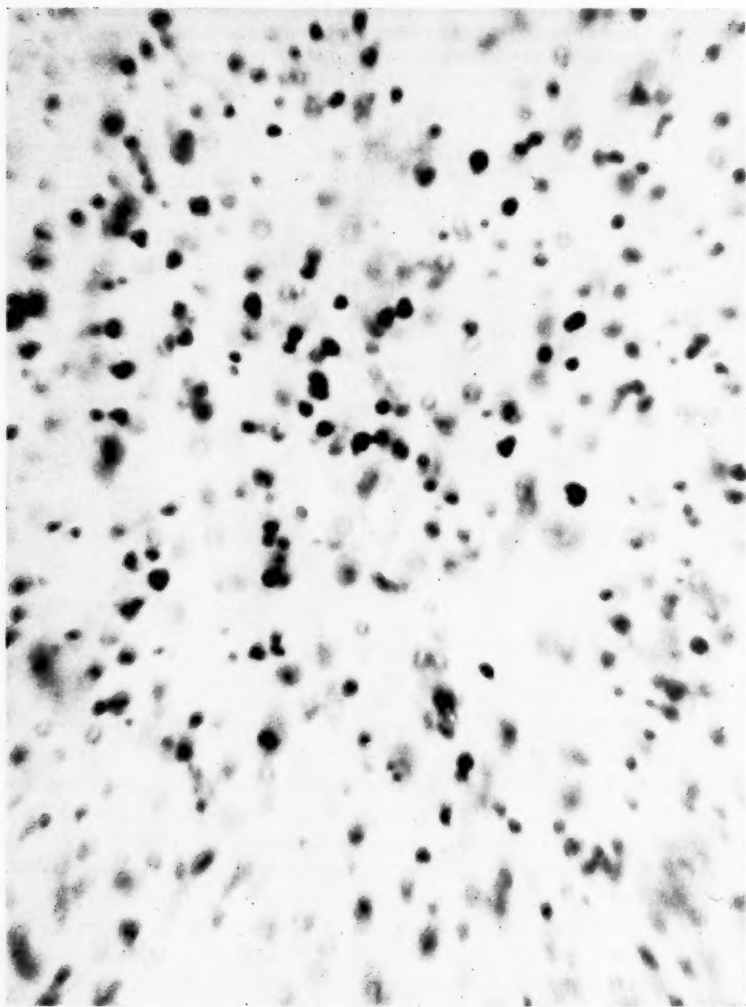


Fig. 3. Radioautograph on x-ray film of P³² tagged chicken erythrocytes ($\times 1280$).

animals that received the activated sheep red cells likewise showed a very small degree of activity of the antiserum ranging between 0.9 to 3.18 counts per minute per ml. However, this radioactivity was shown to lie entirely within the supernatant serum following the extraction of the antibody by normal nonradioactive antigen. There was no radioactivity found in the antibody portion of the serum.

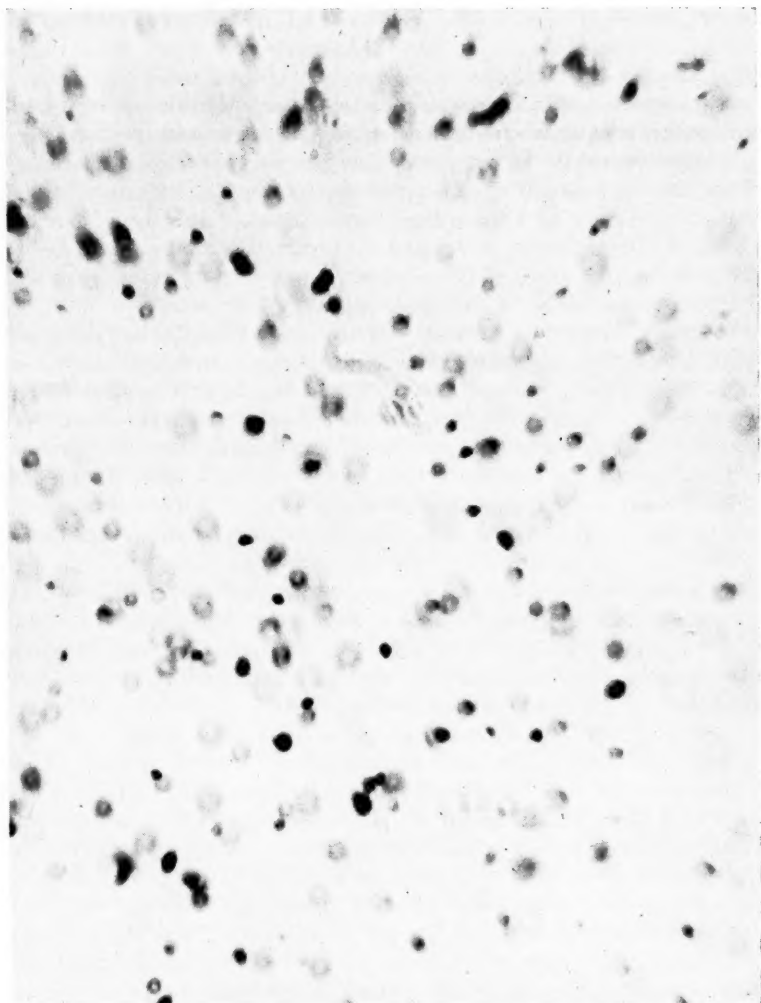


Fig. 4. Radioautograph on x-ray film of smear of P³² tagged sheep erythrocytes ($\times 1280$).

DISCUSSION

The plan of procedure in this study consisted of an attempt to detect radioactivity within the antibody portion of serum formed in response to the introduction of a radioactive-tagged antigen into the body of an experimental animal. P³² labeled erythrocytes were utilized as antigen, and the specific hemagglutinin produced was studied for radioactivity content. By this method of approach it was felt that perhaps some further data

could be obtained regarding the problem of whether or not portions of an antigen constituted an integral part of the antibody molecule. The hemagglutinin portion of the antiserum was isolated by its *in vitro* action of becoming bound to specific antigen added to the serum. When normal non-activated erythrocytes entered into an *in vitro* antigen-antibody reaction with antiserum and the antigen-antibody complex was separated and assayed, any radioactivity found within the resultant agglutinated red cell mass can be assumed to arise from the hemagglutinin portion. Thus the origin of any radioactivity content found within the antibody may be attributed to the presence of P³² (tagged erythrocyte antigen) and not due to radioactivity within the medium or in extraneous material.

Antibody protein has been successfully labeled²⁶ *in vivo* with isotopic N.¹⁵ It has been shown that the *in vitro* introduction of radioactive isotopes into antibodies did not destroy the serologic specificity or ability of the precipitins,²³ agglutinins,⁵ or antitoxin flocculating antibodies⁶ to enter into specific reactions with their corresponding antigens. In a similar manner protein antigens have been tagged with radioactive phosphorus¹³ and iodine,¹⁰ with the retention of their ability to react with specific antiserum.

The hemagglutinin was studied, since this antibody is readily produced and lends itself to isolation as an antigen-antibody complex. This agglutinated cell mass consisting of erythrocytes coated with or held together by bound hemagglutinating antibodies can be easily separated and assayed. The rat produces a high titer of hemagglutinins within five days following the intravenous injection of a single dose of foreign erythrocytes, and this time interval is well within the half-life of 14.3 days for P³². Therefore, should any of the P³² erythrocyte antigen complex be incorporated into the antibody being synthesized, its radioactivity content could be easily measured. Roberts, Adams, and White²⁴ found that saline extracts of tissues from nonimmune mice and rats possessed relatively high agglutinating activity. However, these nonspecific agglutinins were not found in normal rat serum either in their report or in our experience. It is well known that ionizing radiation will depress antibody formation.⁸ However, there was no appreciable difference in the hemagglutinin titers of those rats receiving P³² activated erythrocytes and control animals receiving nonactivated cells. The explanation for this is not evident, except perhaps that the dosage given each animal was not sufficient to produce this effect.

The possibility that free P³² might diffuse from the erythrocyte into the plasma shortly after its intravenous administration and mask the results seemed unlikely, since it has been found that labeled phosphate ions within a short time after their entrance into the red blood corpuscle participate in intracellular phosphorylation processes and are thereby removed from the inorganic fractions. Therefore, the percentage chance that P³² atoms move from the cell into the plasma is appreciably smaller than movement in the opposite direction. The P³² content of the erythrocyte, consequently, remains practically constant for some time.^{17a} However, should any unbound

P³² escape into the plasma, it is not likely that significant amounts would remain there free for any length of time in the dosage here employed.^{10d} Hevesy^{17b} found in distribution studies in the rat that the greatest percentage of labeled phosphate accumulated in the skeleton. Cohn and Greenberg⁷ found that retentions of radiophosphorus in rat tissue decreased in the following order: bone, liver, gastrointestinal tract, heart, kidney, lungs, blood, muscle, skin, and brain, with less than 0.15 per cent found in the blood after forty hours.

Radioactive assays of the erythrocytes used as antigen reveal that these cells had been activated to a significant degree. Activity measurements of the saline used in washing the cells show that the radioactivity resided within the red cells. The studies of Eisenman and co-workers,¹¹ Taylor et al,²⁷ and Gourley and Gemmill¹⁴ seem to indicate that when erythrocytes are activated with P³² at incubation temperatures similar to those here employed, the passage of the phosphate ion into the cell is due to a chemical or enzymatic process rather than simple physical transfer or diffusion.

The radioautographs of smears of these erythrocytes (Figs. 3 and 4) show that the radioactivity was within the erythrocyte itself. However, the validity of any conclusions drawn from the results of this study depend on the assumption, of which there is no definite proof, that phosphorus in entering the cell either enters into chemical combination or becomes absorbed or adsorbed to that portion or portions of the cellular structure that are antigenic and responsible for the production of hemagglutinins. The red blood cell is indeed a complex antigen, and in fact probably consists of multiple antigens. The chemical composition of the erythrocyte²⁸ consists of hemoglobin (globin and a ferrous complex of protoporphyrin), the dried substance of the stroma containing protein, phospholipids, cholesterol, neutral fat, sulfhydryl groups, adenine-ribose nucleotide, and minerals. Just what portion or portions are responsible for the antigenicity of the red corpuscle is not known. Hemoglobin is weakly antigenic, and antisera may be obtained by immunization with prepared erythrocyte stromata. It is therefore noteworthy to point out that Erf and Lawrence¹² found radioactive phosphorus in the hemoglobin fraction and small quantities in the stroma of activated red blood cells.

Two different and distinct types of red cells were used as antigen, nucleated chicken erythrocytes and sheep erythrocytes representing the non-nucleated type of red cell. The possibility was kept in mind that in activating each of these types of cells the phosphate ion perhaps enters a different cellular portion that may be antigenic in each instance. The exact site of tagging with P³² in each case is not definitely known.

Activity measurements of the antibody portion of the serums of rats that had received a radioactive antigen showed no degree of radioactivity and were equivalent in this response to the antibody portion of the serum of control rats who had received a similar but nonradioactive antigen.

Although definite proof is not presented that the antigenic portions of the chicken and sheep erythrocytes were tagged with radioactive phosphorus, the inability to find radioactivity within antibody formed in response to the administration of a radioactive-tagged antigen certainly can add no support to the theory that antigen is incorporated as an integral portion of the antibody molecule.

SUMMARY

1. Sheep erythrocytes and chicken erythrocytes were tagged *in vitro* with P³² and employed as antigens.
2. Ten rats received radioactivated chicken erythrocytes and ten activated sheep erythrocytes. Ten rats served as controls, receiving normal non-activated red blood cells.
3. The labeling of erythrocytes with P³² in the dosage employed did not interfere with either the production or the immunologic specificity of the resultant hemagglutinin.
4. The hemagglutinin portion of the resultant antiserum was isolated as an antigen-antibody complex with normal nonactivated species specific erythrocytes and assayed for radioactivity. No radioactivity was found in the antigen-antibody complex.
5. The failure to find tagged portions of the erythrocytes within the hemagglutinin therefore fails to present any evidence in favor of the theory that antigen is incorporated into the antibody molecule during antibody synthesis.

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CANADIAN SOCIETY FOR THE STUDY OF ALLERGY

The annual meeting of the Canadian Society for the Study of Allergy will be held at the Mount Royal Hotel, Montreal, on Tuesday, June 19, 1951. The morning session will feature "Patch Testing in Cases of Contact Dermatitis" by P. A. Ryan, M.D., Toronto; "Studies in Experimental Hypersensitivity—Some Effects of Cortisone on Morphology and Metabolism" by Drs. J. D. L. FitzGerald and Chester McLean, Toronto; and a round table discussion on "Difficulties and Failures in the Treatment of Asthmatics" by Drs. H. S. Mitchell, C. H. A. Walton, H. Bacal, and Mary S. Young.

In the afternoon the following papers will be presented: "Cardiac Asthma" by Jonathan C. Meakins, M.D., Montreal, the guest speaker; "The Use of a Combined Antihistamine and Antigen in Hyposensitization Therapy" by Jacques Leger, M.D., Montreal; "The Treatment of Dysmenorrhoea by Antihistamines" by Cluny MacPherson, M.D., St. John's; "Food Allergy as a Factor in Personality" by R. F. Hughes, M.D., F.A.C.A., Hamilton; and "Psoriasis—an Allergic Disease" by K. A. Baird, M.D., F.A.C.A., West St. John.

All American allergists are cordially invited to attend.

EXPERIENCES WITH ACTH AND CORTISONE IN THE TREATMENT OF ASTHMA AND ECZEMA IN INFANCY AND CHILDHOOD

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THERE are now in the literature a number of publications concerning the use of ACTH and cortisone in allergic diseases of adults, particularly in bronchial asthma. The literature of this subject has been recently thoroughly reviewed by Segal and Herschfus.⁵ In the field of pediatric allergy we have been able to find but one report, that of Kanee et al.⁴ This concerns a fourteen-month-old boy with asthma and eczema whose skin lesions had failed to respond to hospitalization and the usual methods of treatment. Satisfactory relief was obtained by the use of ACTH injected intramuscularly.*

Our series comprises thirteen children ranging in age from eighteen months to fifteen years. Three suffered principally from eczema and ten from bronchial asthma. All children, except one of the asthmatic infants, had been thoroughly studied from the standpoint of pediatrics and allergy without relief, and their condition was such that in any case hospitalization would have been necessary. The patients were hospitalized for a control period of seven to ten days, when possible, to see how their difficulties would respond to simple change of environment and the usual methods of treatment. Placebos were not used in this study, with but one exception, because we had had sufficient experience with adults seen in consultation, in whose cases such studies had been made, to be convinced that these preparations are potent therapeutic measures in the diseases treated.

During the preliminary period of hospitalization several Thorn tests⁶ and routine complete blood counts were made. The children were weighed and the blood pressure was taken every other day. The following blood chemistries were routinely determined: total protein; albumin-globulin ratio; serum chlorides, sodium, potassium, sugar and CO₂ combining power. Glucose tolerance tests and urea clearance tests were also commonly done. During the course of treatment the same determinations, with the exception of the latter two and the Thorn tests, were also made twice a week or oftener. Absolute eosinophile counts were made every other day.

Five of the children were continued on ambulatory therapy. It was carefully explained to their parents that the results of long-term treatment with

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*Since this article was submitted for publication two articles have appeared on the subject of the treatment of atopic dermatitis in children with ACTH: Randolph T. G., and Rollins, J. P.: *Ann. Allergy*, 9:1 (Jan.-Feb.) 1951 and DiGeorge, A., and Nelson, W. E.: *J. Pediat.*, 38:164, (Feb.) 1951.

these hormones are not known, and they were required to sign a release to the effect that they clearly understood this and accepted full responsibility for any untoward effects. The fact that without exception they were glad to do this highlights their desperation. On ambulatory therapy the patients visited the office weekly, at which time they were weighed and examined physically; a urine examination and total eosinophile count were made, and the blood pressure was taken. All were kept on low salt diets and given potassium iodide in the case of the asthmatic patients and potassium chloride in the case of the eczematous patients. They were weighed at home every two days, and the blood chemistry was checked every two or three weeks.

In this communication two illustrative cases will be reported in detail, and a brief summary of the others will be given.

Case 1.—This boy was first seen at the age of three months. Eczema, which was severe and involved practically the entire body, had been present since the age of three weeks. A milk-free diet, environmental control, and other measures gave temporary relief. However, by the time he was eight months of age no obvious progress was being made; and since his skin was too generally involved for direct testing, passive transfer tests were carried out. The application of information obtained by these tests resulted in some improvement for a time. However, bronchitis accompanied by wheezing developed, his skin became progressively worse, and at the age of fourteen months he was hospitalized. The eczema cleared remarkably well, and he was discharged after eight days. It was felt that the improvement was due to environmental control, and special efforts were made to provide a room as allergenically clean as possible at home, before discharge.

After a week at home the eczema became much worse, and he was hospitalized for ACTH therapy. He was then fifteen months of age. ACTH in doses of 2.5 mg every six hours was administered by intramuscular injection, and after twenty-four hours the dosage was increased to 5 mg. When he did not improve in the subsequent forty-eight hours, the individual doses were increased to 8 mg. This was continued for seventy-two hours, and his absolute eosinophile count, which had been 17,280 per mm³ on admission, dropped to 180. His skin improved steadily thereafter, and he was discharged after eleven days of hospitalization, having received a total of 179.5 mg of ACTH. His skin was almost clear. He had lost 120 gm during the period of hospitalization.

The skin gradually became worse again, and at the age of seventeen months he was readmitted to the hospital. The skin was not improved after a trial period of nineteen days, so ACTH in doses of 10 mg was administered every six hours. After two days the skin cleared remarkably and on the third day was almost completely clear. He was discharged on the twenty-sixth hospital day after having received a total of 270 mg of ACTH. He had gained 300 gm (10 oz) in weight. The mother had been instructed how to administer ACTH at home, and he was carried along on 10 mg doses every six hours for a week. The skin remained clear, and the dose was reduced to 10 mg every eight hours. On this dose the skin again became worse, and it was decided, because we were rather timid about continuing at home for a prolonged period on ACTH, as this was our first experience with ambulatory therapy, to discontinue this medication. In the two weeks at home he had received a total of 470 mg. It was noted that while under ACTH therapy, both in the hospital and at home, the child was distinctly euphoric.

Six weeks later, at the age of twenty months, the skin was again severely eczema-

tous. At this time an ointment was prepared containing 500 mg of cortisone mixed with 20 gm of Hydrosorb (Abbott) and 40 gm of Lassar's paste. A similar ointment was prepared as a control without the cortisone. The mother was given both ointments to try, but she was not told which contained the cortisone. After a week's application there was no significant improvement, and the side of the body to which the cortisone ointment had been applied was, in the mother's opinion, somewhat worse than the control side. These ointments were then discontinued.

Three weeks later the skin had improved somewhat, and this continued until at the age of two years it was sufficiently clear so that direct testing could be done. Guided by the information so obtained, changes were made in the diet, and his improvement has continued.

Comment.—As is well known, infants have a definite tendency to recover spontaneously from eczema, although unfortunately this cannot be predicted with certainty. The use of ACTH in this, as well as in other cases, has appeared to help the child through difficult periods until the healing forces of nature can assert themselves. In this particular case, also, the use of ACTH, by relieving the child's eczema although temporarily, helped a very difficult family situation wherein a doting grandfather was almost psychotic because of his grandchild's condition. The failure of the cortisone ointment cannot be considered conclusive, particularly since it has been shown by Bordley¹ that cortisone locally will reduce polyps arising from allergic mucous membranes. Further work needs to be done with the use of cortisone locally on the skin.

Case 2.—This girl was first seen at the age of three months because of atopic dermatitis, which responded well to intensive pediatric and allergic management. At the age of fourteen months she had her first attack of bronchial asthma. Attacks have recurred at intervals ever since. They occur without infections but are usually worse when preceded by respiratory infections. Between the ages of seventeen and nineteen months she had severe uncontrollable attacks while at home, requiring three hospitalizations.

At the age of twenty-one months this girl was admitted to the hospital and started on ACTH, 2.5 mg every six hours (10 mg daily). When no relief was obtained after three days, the dose was increased to 20 mg daily. After three days of this treatment the chest cleared completely, and the following day the dose was reduced to 10 mg. per twenty-four hours. Two days later she developed acute bronchitis accompanied by fever, and the drug was discontinued. She was treated with penicillin and sulfonamide compounds, did not develop asthma, and was discharged on the twelfth hospital day, after having been afebrile for four days. Previous to the onset of the respiratory infection she had received 110 mg of ACTH over a period of ten days.

Twenty-four hours after discharge she again became asthmatic and eight days later was readmitted to the hospital. This time she was started on cortisone by intramuscular injection, 50 mg twice a day, on which she cleared after two days. The dose was then reduced to 50 mg once a day for six days. She continued free from asthma and was discharged on the fifteenth hospital day, having received a total of 500 mg of cortisone over a period of eight days.

Following discharge she remained free for eleven days, when she developed a respiratory infection followed by asthma which has persisted intermittently since then. Up until the time of this writing she has been on ACTH at home continuously with doses varying from 20 to 40 mg per twenty-four hours. She has continued to have attacks of asthma, which the mother relieves as far as she can by the use of symptomatic medication, particularly aminophyllin suppositories and the subcutaneous injection of epinephrine, the mother using just enough ACTH to keep her under control with the help of these medications. The child has felt well in general, and

ACTH AND CORTISONE IN ASTHMA—GLASER ET AL

her appetite has been exceedingly good. She has gained 1 kg over a sixty-two-day period at home during which she received 1729 mg of ACTH.

Comment.—This case illustrates the fact that the control of asthma by ACTH is quantitative. This child's asthma could be completely controlled by ACTH, but because of the expense of this drug the mother uses only as much as is necessary to keep the girl under control by the accessory employment of epinephrine by injection and aminophyllin rectally. This patient, like all other patients under treatment with these hormones, is being constantly studied and rechecked and given such injection treatments as appear to be indicated because of her asthma with the hope that ultimately her allergic condition will be relieved without the necessity of hormone medication.

In addition to the first of the two cases above reported, two other children with eczema were studied. One was a girl hospitalized at the age of twenty-three months because of severe generalized eczema. On ACTH therapy she cleared nicely for a time but while clearing developed an attack of bronchial asthma. This suggests that larger doses are required in the same patient to relieve asthma than eczema. This is corroborated by a similar experience in an adult patient, but before a general rule of this nature can be established many more cases will have to be studied. When the girl's skin had cleared sufficiently, direct skin testing was done. This corroborated the results of passive transfer tests done with blood serum obtained just before hospitalization. The skin remained clear for about eleven days after discharge, when she became gradually worse in the course of a few days and appeared almost as bad as when first hospitalized. However, she thereafter has responded very satisfactorily to pediatric-allergic management.

The other eczematous child was a congenital deaf mute fourteen years of age with severe, generalized, chronic, atopic dermatitis which in recent months had been accompanied by severe mental depression. She was hospitalized for cortisone therapy and cleared nicely over a period of twenty-nine days during which she had received a total of 4050 mg. With the clearing of the skin the mental depression disappeared. She remained well three weeks at home without hormone therapy, following which her skin and mental condition rapidly reverted to the same state as before hospitalization.

Among the nine remaining cases of bronchial asthma were two boys, ages nineteen months and three years, respectively, who were admitted to the hospital critically ill in severe status asthmaticus. In addition to the measures usually employed,³ each was given 100 mg of cortisone intramuscularly upon admission. While these children made nice recoveries, it cannot, of course, be stated that this was due to the cortisone. However, because of experience with adults seen in consultation critically ill in status asthmaticus who had not responded to any form of therapy until cortisone was used, we feel that it might have helped these children. In our opinion it should be given to all children in severe status asthmaticus. We feel that under such circumstances cortisone is preferable to ACTH

because there is no opportunity to determine whether or not the adrenal glands are capable of responding to stimulation following the injection of ACTH. It should be pointed out that the relatively large dose of cortisone given these children, 100 mg each, is half the dose customarily given to adults the first twenty-four hours of treatment with cortisone. These large doses were given because the infants were critically ill, and it is generally accepted that the dose should be in proportion to the severity of the illness and not the age or weight of the child. There is, however, probably a great difference, as far as danger to the patient is concerned, between giving an occasional large dose and continuous treatment with this steroid.

The remaining cases of asthma may be briefly reported as follows:

1. A fourteen-year-old girl returned to Rochester from Denver, where she had been a patient at the National Home for Jewish Children because of intractable asthma. She had been free from attacks for about a year. Almost immediately on returning to Rochester she developed an attack which gradually became uncontrollable at home, so she was hospitalized. She was given 560 mg of ACTH over a period of eleven days and made a nice recovery. On discharge she returned immediately to Denver by airplane. Her remission lasted three weeks, following which she again began having mild asthmatic attacks.

2. A seven-year-old girl who had had bronchial asthma since the age of thirteen months was admitted in severe status asthmaticus and responded well to a total of 420 mg of ACTH over a period of nine days. She remained free from asthma for five weeks, when she developed a severe attack without any known precipitating cause and since then has continued to have occasional minor attacks.

3. A nine-year-old boy who had had asthma since the age of three and a half years, perennial but worse during the ragweed pollen season, entered the hospital in severe status asthmaticus from which he obtained relief following the administration of 120 mg of ACTH over a period of six days. Asthma recurred the day after discharge; he was readmitted and did well on ACTH, 185 mg being administered over a period of eight days. This was continued at home until the end of the ragweed season. A dose of 10 mg. every six hours was required. At the end of ragweed season the ACTH was discontinued, as the mother could then control the attacks at home with symptomatic remedies.

4. A thirteen-year-old girl with perennial bronchial asthma since the age of two and one-half years was admitted in severe status asthmaticus. She was discharged with a clear chest after eleven hospital days during which she had received 180 mg of ACTH. After three days at home free from asthma she was again admitted in severe status asthmaticus and this time was started on cortisone. She was given 625 mg over a period of nine days. A week after discharge the attacks recurred but could be kept under control by symptomatic medication.

5. A nine-year-old boy with perennial asthma since the age of fifteen months was admitted in severe status asthmaticus and responded well to 200 mg of ACTH administered over a period of twelve days. He gained 3.5 kg during that period. He remained free from asthma for four months, which is the longest remission in our series. The longest remission yet reported was that of an adult in the series of Carey et al² who was symptom free for ten months following ACTH therapy. Since no controls can be applied to cases of this nature and since spontaneous re-

ACTH AND CORTISONE IN ASTHMA—GLASER ET AL

missions do occur in chronic asthmatics, the evidence is only presumptive that remissions of this length are due to the hormone therapy.

6. A two-year-old girl who had had perennial bronchial asthma since the age of eight months following virus pneumonitis was hospitalized. She did well on 95 mg of ACTH administered over a period of six hospital days. However, three days after discharge she again developed status asthmaticus, and recovered on 225 mg of cortisone administered over a period of six hospital days. This time she remained free from asthma for fifteen days, following which she again developed asthma precipitated by an acute respiratory infection, was hospitalized, and did well on a total of 140 mg of ACTH administered over a period of seven hospital days. Since discharge she has been controlled at home on doses of ACTH varying from 40 mg to 10 mg per day. At the time of this writing she had received 1154 mg of ACTH over a period of seventy-six days.

7. This child developed asthma at the age of five months. Between the ages of sixteen and twenty-six months she had had three hospitalizations because of asthma. At the age of thirty months she was hospitalized in severe status asthmaticus and did well on a total of 210 mg of ACTH over a period of twelve days. She was continued at home on doses of ACTH varying from 2.5 mg three times a day to 5 mg four times a day, depending upon the amount necessary to keep her under control with minimum accessory symptomatic medication. She had received a total of 512.5 mg of ACTH over a period of forty-eight days when the medication was discontinued. However, hospitalization was again necessary because of asthma six days later, and this time she did well on a course of 400 mg of cortisone over a period of eight days. On discharge she remained comparatively free from asthma for a period of thirty-nine days, her longest remission.

Hospitalization was again necessary because of a very severe attack of asthma which developed after playing in a pile of dead leaves. After eight days she was discharged with a clear chest after having been given 560 mg of ACTH. At the time of this admission it was observed that she had gained considerable weight (3.5 kg) over the forty-nine-day period since discharge from her previous hospital admission. She also had what appeared to be typical striae albicantes in the interscapular spaces. These disappeared, however, although the ACTH injections were continued. It was necessary to continue the ACTH at home to keep the asthma under control, and dextro-amphetamine sulfate (Dexedrine) was administered to curb her appetite. Over a period of fifty-six days from discharge she was given 1215 mg of ACTH. She was then tried on oral cortisone over a period of sixteen days and controlled by one 25 mg tablet three times a day. She had, however, gained 2.6 kg over a period of seventy-two days, and it is planned to drop the hormone medication and hospitalize her if necessary for asthma without hormone therapy until her normal weight is reached.

SUMMARY AND CONCLUSIONS

It would be highly presumptuous in a series as small as this (thirteen children with eczema and asthma) to draw any definite conclusions. However, we believe that as a result of our experience the following statements may tentatively be made:

1. Both ACTH and cortisone are potent agents in the *temporary* relief of chronic atopic dermatitis (eczema) and bronchial asthma in infancy and childhood.

2. Infants and children react to these hormones essentially as do adults except that they require larger doses in proportion to their body weight.

The dose of the drugs, within limits yet to be determined, depends upon the severity of the disease and not upon the age or weight of the child.

3. The response to these drugs, at least in asthma, is quantitative; i.e., the worse the disease, the more of the drug is required. This fact alone is sufficient to make mandatory a complete study of the patient from every standpoint, particularly that of allergy, because the greater the load that can be lifted from the patient by specific management, the less will be the amount of hormone therapy required. This is important not only because of the cost of these preparations but because of possible deleterious effects of the use of these drugs over long periods.

4. ACTH and cortisone do not interfere with the results of the immediate wheal type of reaction as commonly employed in skin testing with the customary allergens. It is therefore possible temporarily to clear up the skin of a patient with eczema, for example, and test the skin directly or relieve the patient with severe asthma so that skin testing and other procedures may be done without undue suffering on the part of the patient.

5. The longest remission in our series of asthmatic children occurred in a nine-year-old boy who remained symptom free for a period of four months after stopping ACTH therapy.

6. No ill results of any significant degree or duration were seen in this study except possibly in one instance where there was an excessive weight gain.

7. We believe that without these drugs the eleven patients here reported who had been unsuccessfully studied and treated for chronic allergic disease would have required interminable periods of hospitalization or would have been obliged to try the uncertain effects of a change of climate. *It is, however, our opinion that these drugs possess great potential for harm as well as good and in the present state of our knowledge should be used only when absolutely necessary. The patient should be kept at all times under the closest supervision.*

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A THEORY FOR ALLERGY AND EXPERIMENTAL EFFECTS OF ANTIHISTAMINES ON THE COMMON COLD

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"COLDS" are said to be affected by everything, from the patient's state of mind to the climate and the time of the year, as well as his contact with virulent organisms or irritating inhalants. In view of this and the subjective character of most reports, it is not surprising that there should be disagreement about the efficacy of antihistamines in the prevention and cure of "colds."^{4,21} To make the problem of antihistamines more complicated, it seems that some people obtain relief from nasal congestion with a certain type of antihistamine yet may not obtain relief from one which may be much more efficacious for still another individual. This may depend on the sensitivity of either the type of cold or the type of individual to adrenergic and cholenergetic stimulation and inhibitions.

To further confuse the picture, the so-called "common cold" is, as a rule, an ill-defined condition involving all types of nasal congestion and catarrh, both acute and chronic. Antihistamines can hardly be expected to be equally useful for such a wide variety of conditions, although histamine or a histamine-like substance has been recovered from the nasal secretions of individuals suffering from both allergic colds and from infectious colds by Kerr and his coworkers.²³ The designation "a cold" undoubtedly comes from the age-old recognition of the fact that overcooling of the body, whether due to exposure to inclement weather conditions, a simple draught, or wet feet often precipitates an upper respiratory condition.¹³ This condition consists primarily of occlusion of the nasal passages and a nasal discharge. It seems wise for the purposes of this paper to designate "the cold" as the layman does, i.e., to call it the syndrome of stuffy nose and nasal catarrh. Then it can be divided into its two main types, and such symptoms as sore throat, fever, malaise, cough, sneezing, et cetera, can be added or subtracted as the case may be. If colds are defined in this general way we shall be better able to understand the reports of the effects of antihistamines upon them. After all, without a careful medical history, nose examination, and culture studies it is impossible to tell one cold from another, and even then many colds remain unclassified. In this report, by an infectious cold is meant any microbial invasion of the nose as well as the condition described by Dochez, Kneeland, and their co-workers as a two-day or three-day virus infection which conveys temporary immunity

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and which sometimes goes on to secondary infection (sinusitis).⁵ By an allergic cold is meant a tissue reaction in the nose of a noninflammatory type which will be described in more detail below. Undoubtedly, there are mixed allergic and infectious colds.



Fig. 1. Vasomotor rhinitis in a cat created by cutting the cervical sympathetic trunk on the left. Cross-section through the nose and anterior ethmoid sinuses ten days later. Note edematous swelling and secretion on the left side of the cat (right in illustration) and appearance of normal side. Compare with Figure 2b.

The rhinologist usually divides well-developed catarrh and stoppage of the nose into one of two main groups, according to the appearance of the nasal mucous membrane. The infectious group is usually a darker red than normal, while the so-called vasomotor or "allergic" group is paler than normal. Jarvis¹⁶ reported several years ago that the pale type of mucous membrane was probably due to overaction of the parasympathetic nervous system, and that all colds can be broadly classified according to their involvement of the involuntary nervous system, but we must be careful to remember that he was describing fully developed nasal conditions in their later stages. However, Jarvis' classification is useful in consideration of the effects of antihistamines and their effect on the cells involved by the autonomic system, and is not as unreasonable as might at first appear.

That the allergic type of cold involves blocking of sympathetic impulses

EFFECTS OF ANTIHISTAMINES—FOWLER

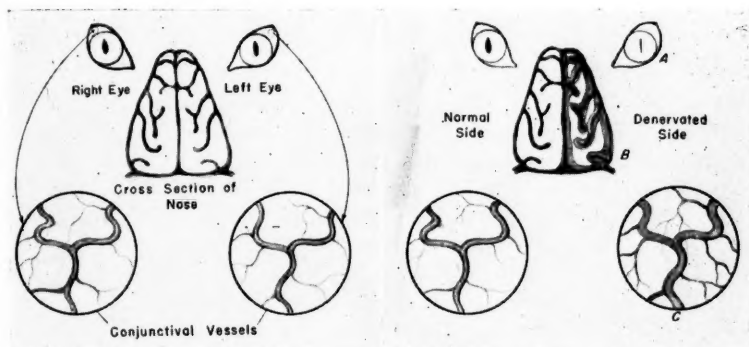


Fig. 2. (a) (left) Diagram of nose, pupils of the eye, and small blood vessel circulation in the conjunctiva. Normal cat. Arrows indicate vessels examined lateral to limbus in the eyes. Magnification $\times 50$. (b) (right) Diagram of nose, pupils of the eye, and small blood vessel circulation in cat after left cervical sympathectomy. Compare with Figure 1. Note (A) Horner's syndrome on the left side of the cat, (B) increased edematous turgescence of turbinates and nasal and sinus mucous membranes, and (C) dilatation of small vessels in the conjunctiva. The same sort of congestion seems to occur with local application of histamine.

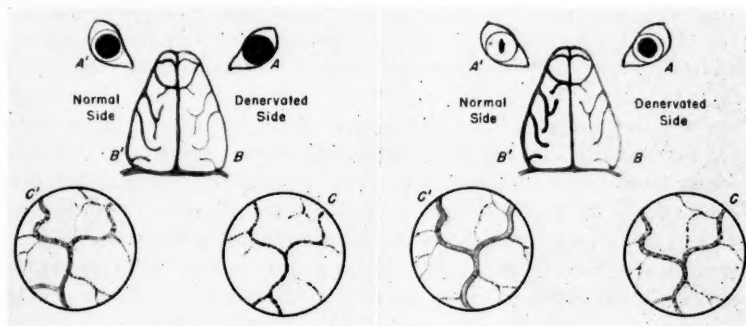


Fig. 3. (a) (left) Sensitization from denervation. Note the effect of 1:1,000 Adrenalin ($\frac{1}{2}$ cc intravenously) on (A) the pupil of the eye, (B) the turgescence of the nose, and (C) the small blood vessel circulation. Note that the greatest effect is on the denervated side, but that near maximal effect is also seen on the normal side. The black specks represent blood sludge. (Knisely¹⁷) Cf. Figure 4. (b) (right) Sensitization to 1:1,000,000 Adrenalin ($\frac{1}{2}$ cc intravenously). Note that there is no effect on normal pupil and very little effect on conjunctival vessels or normal side of nose. Note considerable effect on denervated, and thus sensitized, left side of cat. A similar picture is obtained with intravenous Pyribenzamine, 25 mg.

to the mucosa and submucosa of the nose is quite definite experimentally (Fig. 1). By cutting the cervical sympathetic trunk or injecting¹² the stellate ganglion with procaine, a typical picture of what is called "allergic vasomotor rhinitis" can be produced in the nose. Thus, in a given individual, the appearance of the allergic state can be produced unilaterally

by ablating cervical sympathetic impulses. The normal side can be used as a control. On the denervated side, there appears a boggy membrane and copious watery discharge. At first the mucosa is quite red. The pale, pinkish gray appearance begins to develop within twenty-four hours and becomes more marked later. After ten days or so, the increased secretion on the operated side is particularly striking if the patient is exposed to mild physical stimuli, such as a draught or a piece of ice held in the hand. In three individuals we have even observed a high eosinophil count in the nasal secretion confined to the denervated side, using Hansel's technique.¹⁵ That the typical appearance of a localized allergic state and hypersensitivity of an organ can be produced surgically by interference with the sympathetic nerve supply, seems a most important fact that must be considered in studying "allergic colds" or for that matter any other allergic phenomenon. It should be useful in the study of antihistamines (Fig. 2).

According to the Law of Denervation as documented and clarified by Cannon and Rosenbluth,³ total or partial blocking of the cells supplied by the sympathetic or parasympathetic nervous system makes them more susceptible to any stimulus, but extraordinarily susceptible to their normal stimuli (Fig. 3). A hypersensitivity of denervated tissues had been suggested by Claude Bernard in 1880¹ and confirmed by many others since, particularly in the pupil of the eye¹⁸ and in the small blood vessels⁷ (Fig. 4). The fact that to a lesser degree hypersensitivity of tissue can also be demonstrated with *partial* blocking of its nerve supply must be of paramount importance in allergic states. If we assume that the allergic state of a tissue or an individual can be produced by reducing the activity of the sympathetic division of the autonomic nervous system and that then various stimuli, such as small quantities of histamine, can work on the affected tissue comparatively unopposed, we have an excellent explanation as to why the stimuli which clinically produce the symptoms of allergy range all the way from the antigen-antibody reactions of a protein to physical stimuli, such as light, heat, or cold, and may even be purely psychic.

In considering overactivity of one division or the other of the autonomic system from denervation or from direct stimulus, especially in considering the effect of drugs on the nose and their rôle in colds, it must not be forgotten that continued overstimulation of a nerve can produce the same end-result as the cutting of that nerve. This was demonstrated by certain experiments in which we had stimulated the cervical sympathetic trunk of cats four or five times in an afternoon at fifteen-minute intervals with $\frac{1}{2}$ volt of 60 cycle alternating current for 30 seconds with a bipolar electrode. All of the cats, with excessive stimulation of the cervical trunk, finally developed Horner's syndrome and blocked allergic-looking noses on the affected side (Fig. 1). A similar effect followed continuous stimulation after burying the leads of a secondary coil in the neck of a cat, with contact on the cervical sympathetic trunk maintained with surgical bone wax.

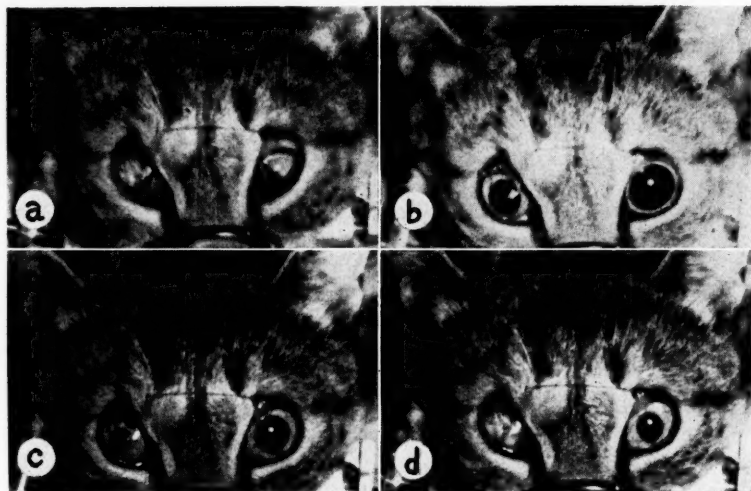


Fig. 4. The paradoxical pupil phenomenon which with similar action of the nictitating membrane clearly demonstrates the Law of Denervation as cited by Cannon and Rosenbluth.³ Compare with Figures 2 and 3.

- (a) Cat under nembutal anesthesia ten days after left cervical sympathectomy.
- (b) Same cat after $\frac{1}{2}$ cc of 1:1,000 Adrenalin hydrochloride intravenously.
- (c) After $\frac{1}{2}$ cc of 1:10,000 Adrenalin intravenously.
- (d) After $\frac{1}{2}$ cc 1:1,000,000 Adrenalin intravenously.

The cat was placed in a brass cage with a primary current sufficient to dilate the eye continuously. The production of this sympathetic paresis was quite the opposite effect from what was intended, but these experiments were quite informative because they parallel the similar findings that occur if the sympathetic end organs are poisoned by overuse of medication, which can overstimulate and therefore paralyze the sympathetic system. The clearest example of this is in the use of strong nose drops over an extended period.⁹ A similar type of massive edema is seen in epinephrine-fast individuals and in the lungs of guinea pigs killed by large doses of epinephrine. Paresis of the sympathetic or parasympathetic by overstimulation may cause sensitization according to the Law of Denervation as stated by Cannon and Rosenbluth,³ and this is a phenomenon which must be considered in assessing allergic states. The observations of Yonkman et al²⁵ and Staub²² suggest that these reactions concern histamine and can be modified by antihistamines (Fig. 5).

It is becoming increasingly apparent that protein sensitivity and the antibody-antigen reaction theories which have dominated the thinking of allergists for years are only a part of the whole story of the allergic cold. Such clear-cut observation as the fact that "hay fever," for example, varies with the pollen count is manifestly important, but even in ragweed hay fever it has recently been shown dramatically by Wolf and his co-workers

EFFECTS OF ANTIHISTAMINES—FOWLER

that psychic stimuli and sympathetic nerve blocks also influence the clinical picture of this type of rhinitis.²¹ I believe that physical and psychic stimuli work on the autonomic receptors and that then various stimuli, from within the body or from without, may produce and modify allergic reactions.¹¹

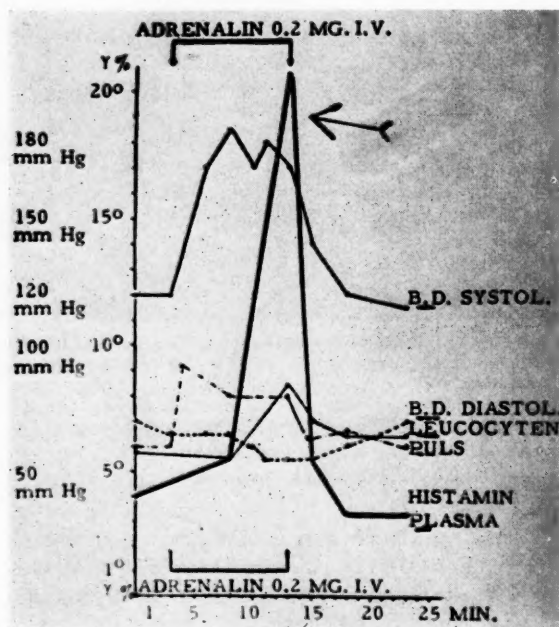


Fig. 5. Release of histamine in the blood after injection of Adrenalin (see arrow). Antihistamine would presumably block or partially block the effect of this histamine if given in large enough doses. B.D. = Blood Pressure. From Staub, Schweiz. med. Wchnschr., 76:818, 1946.

Histamine is apparently a mediator in the development of allergic symptoms and states. Antihistamines seem to modify them. Histamine dilates the capillaries and increases their permeability to body fluids. The typical wheal with subcutaneous injection of histamine which resembles hives, the asthma with aerosol inhalation of histamine in animals⁸ and the recovery of histamine from nasal secretions of humans with allergic colds²³ established it as a definite factor in allergic reactions (Fig. 2b).

The antihistamines are thought to compete in the cell for the same receptors as the histamines, and therefore they tend to prevent histamine action on blood vessels and gland tissues, or ameliorate it if it has occurred.⁶ When applied topically to the meso-appendix of a rat, according to Haley and Harris,¹⁴ most antihistamines in common clinical use produce

EFFECTS OF ANTIHISTAMINES—FOWLER

a reaction similar to, if not as great as, that of a comparable dosage of epinephrine. In our experiments intravenous injection or topical application produced sludged blood and some narrowing of the venules and arterioles and decreased capillary flow in the conjunctiva of cats, just as does epinephrine or cervical sympathetic stimulation.¹⁰ The adrenergic action seems somewhat more marked and more prolonged in ten-day sympathectomized cats, and the edema in the sympathectomized conjunctiva clears appreciably when antihistamines are applied or injected. An adrenergic action could explain an antihistaminic effect in allergic colds. Over extended periods the antihistamines seem to help the pale boggy types of nasal membrane which have been shown experimentally to be due to reduced action of the sympathetic control to the nose and probably involve slow release of histamine. It is possible that antihistamines in the sensitized nose produce an adrenergic potentiation just as they seem to elsewhere,²⁵ and that is one of the actions of some antihistamines in allergy. It is my opinion that a high percentage of all "colds" are allergic, in the sense of the word used in this paper, and that this high percentage contributes materially to the reported success of the antihistamines for the control of "colds" in large unselected groups of people.

But what about the infectious type of cold? Many colds apparently are not basically allergic in the accepted sense. The antihistamines have been reported also to have an effect on this type of cold if they are given early enough.¹⁰ Our ideas on a possible effect of the antihistamines on the early stages of an infectious type of cold are still only by inference, but may be of sufficient value for further study. Some believe that histamine is the most important substance in initiating the inflammatory reaction, cf. Menkin.¹⁹ If this is true, in infectious colds the antihistamines might cause some reduction in the inflammatory reactions. However, it may be against histamine, or a histamine-like substance, in the early invasive stages of infections in the nose that the antihistamines have an effect. Since antihistamines are said to be clinically helpful only in the early stages of a cold, perhaps at that time competition for the cell receptors of histamine is possible, but later, if the cold is severe, the histamine is present in too great a quantity for a reasonable therapeutic dose of antihistamine to have a chance of competing for a given cell receptor.

Viewing the problem from the neurogenic aspect, perhaps the antihistamines delay or reverse the secondary vasodilatation which occurs after the vasoconstriction produced by an exposure to stimuli like a draught or wet feet. The early adrenergic effects of certain antihistamines on infectious colds may be purely symptomatic, similar to the effects of ephedrine or atropine. They produce a drying of the membrane and reduced circulation in the turgid turbinates, and therefore provide temporary relief from the nasal congestion which the patient interprets as a cure of his cold. Many antihistamines are not adrenergic. Their effects, if any, must be on a different stage in the cold. Antihistamines also have a generalized sedative

action and therefore in many ways are comparable to the old-fashioned remedies consisting of barbiturates, aspirin, and atropine. In the long run, prolonged vasoconstriction should make an infectious cold worse, for it is simply recreating the vasospasm and consequently reduced skin and mucosal temperature, which is apparently the first reaction of the body to chilling. There is some clinical evidence that the use of antihistamines does make colds worse; at least many of my patients have the impression that their noses were too dry and that their colds seemed to be prolonged because of the drug.

As mentioned above, with the intravenous and local application of most antihistamines, just as with epinephrine and chilling of the body surface, there is at first a contraction of the precapillaries and arterioles.¹⁴ With Pyribenzamine and Antistine, blood sludge¹¹ develops in the vessels of both the eye and the nose with slowing of the circulation (Fig. 3). If the vasoconstriction persists, there must be consequent drying of the mucous blanket and thus interference with ciliary flow. Blood sludge tends to collect and thrombose in injured areas and in areas where there is tortuosity of the vessels and thus to produce localized areas of ischemia. Any one of these might increase the susceptibility to infection. Whether there is also eventual destruction of the cilia and changes in the epithelium, as with ephedrine and other nose drops, as shown by Proetz²⁰ and others, is not yet proved, nor is increased permeability of the epithelium to bacteria and to viruses; but these are not unreasonable expectations. On the whole, laboratory experiments indicate that therapeutic doses of the common antihistamines would not be expected to be of value in well-developed infectious colds. They might give some help in the early stages of the infectious cold or such colds in which an allergic factor is present.

SUMMARY

It is suggested that "colds" involve overaction of either the sympathetic or the parasympathetic nervous system of the nose, and that since histamine or histamine-like substances are involved in the autonomic balance, antihistamines will sometimes interfere in its action enough to produce symptomatic relief. First, they produce an effect on the peripheral vessels of a stimulant, like epinephrine, and perhaps secondarily as a paralyzing agent, like procaine or atropine. At any rate, they seem to ameliorate the effects of histamine in the allergic type of cold. It also seems possible that the antihistamines must have some effect on secondary processes developing after physical or psychic stimuli which seem to predispose to the infectious type of cold in some people.

The observations seem to indicate that a specific hypersensitivity and imbalance of the involuntary nervous system is fundamental in the allergic type of cold. Histamine or histamine-like substances seem to contribute to the symptomatology. The allergic individual is, apparently, the constitutional type in whom there is a comparatively reduced functioning of the

EFFECTS OF ANTIHISTAMINES—FOWLER

sympathetic response from his autonomic nervous system with overaction of the parasympathetic response. This can be due either to lack of adequate opposition or from sensitization to parasympathetic stimuli. Either could be influenced by antihistamines, which have been shown to have adrenergic (sympathomimetic) as well as atropine-like properties.

Whether one can assume that the individual who develops the infectious cold does so from overaction of the sympathetic side of his autonomic nervous system is not clear in all cases. Certainly there is an increased sympathetic response in some. The theory is presented that when and if the antihistamines have an effect on the infectious cold they block secondary parasympathetic tissue responses in the psychic or physical stimuli stages of certain colds and so produce symptomatic relief. They may also reduce the action of histamine as it is released by infection in the early invasive stages of a mild cold. The adrenergic action of antihistamines may tend to make the later stages of a cold worse.

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(Continued on Page 335)

NATURAL STEROID COMPLEX IN THE TREATMENT OF BRONCHIAL ASTHMA

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THE purpose of this communication is to present the beneficial results seen in a group of severe intractable asthmatic patients treated orally with a natural steroid complex.*

The advent of ACTH and cortisone has stimulated further the quest for other synthetic sterols or natural steroid complexes which might be useful as adrenocortical substitutes^{8,14} or stimulants. Although these agents do not give permanent benefit,⁵ they are quite able to give considerable relief in many chronic collagenous diseases^{4,5,6,9,17} and hypersensitivity states^{1,13} which may be resistant to conventional therapy. The undesirable side effects and complications following ACTH and cortisone are well known.^{19,20} Any preparation which is easily administered, well tolerated, and free from undesirable side actions is well worth study.

MATERIALS

The steroid complex concerned is composed of steroid conjugates which are separated from the estrogen conjugates present in the original material. It contains considerable amounts of the various sterols, including neutral steroids, derived from pregnant mares' urine and present as water-soluble conjugates.

Partitioning and investigation of the sterol conjugates in this preparation are being studied currently. The magnitude of this project is appreciated. It is conceivable that the final studies may take some years to conclude. Partition studies show that after acid hydrolysis of the ether-soluble fraction there are acidic, phenolic, and neutral fractions. The conjugates are present in the form of sulfates and glycuronides which have been separated now from each other. After hydrolysis there are present also steroids of the pregnane type. Fractionation of the neutral material shows it to be made up of ketonic and nonketonic substances. Each of these latter fractions is being subjected to further separation techniques.

The question arose as to whether such preparations had any effect in the collagenous diseases. In experimental animals, using the Seifter technique,¹⁵ Marisone was discovered to possess approximately 50 per cent of the activity of cortisone. More recently, a modification of the Selye "rheumatoid" rat test¹⁶ was employed. This technique consists in measuring quantitatively the edema produced in the ankle joint of the adrenalectomized male rat following the local injection of formalin. Daily pretreatment of the animals with 50.0 mg injections of Marisone gave

*The preparation used was "Marisone" and was kindly supplied by Ayerst, McKenna and Harrison, Ltd., New York, New York.

definite reductions in the amount of edema produced, of an order only slightly less than that found when pretreatment with a 5.0 mg daily dosage of cortisone acetate was used. Pretreatment with a lower dose of Marisone, 10.0 mg daily, caused a measurable reduction of the edema.¹⁸ In these latter experiments, it was found that pretreatment gave a reduction in edema which was equivalent to pretreatment with 25.0 mg of pregnenolone.

The DOCA-like activity of Marisone is not believed to be great in view of the animal, as well as human, studies done to date.¹² Animal chronic toxicity studies show little evidence of any extensive toxicity. Massive doses given intravenously cause no ill effects.

Pilot studies in cases of rheumatoid arthritis were encouraging^{2,3,7} and showed that in some patients the results were very striking, but usually improvement was gradual and not as dramatic as with ACTH or cortisone. In some patients, the sedimentation rates fell slowly but progressively.

In humans there was no increased excretion of the 11-oxycorticoids or the 17-ketosteroids following continued daily doses of 1.0 to 2.0 gm for as long a period as six months. No ill effects have been observed in humans who had been receiving Marisone for over six months. In some adult male patients and in preadolescents of both sexes there may be encountered a slight turgescence of the breasts which rapidly subsides upon the reduction in dosage or cessation of therapy.

Further laboratory work on the effectiveness of Marisone in preventing hypersensitivity reactions in animals is being conducted and will be reported upon separately.

In view of the foregoing pharmacologic effects of Marisone in the collagenous diseases, it was decided to determine its effectiveness in the treatment of human hypersensitivity states, especially in chronic bronchial asthma.

METHODS

Fourteen asthmatic patients from the Allergy Clinic of the Beekman-Downtown Hospital and from private practice were selected because their clinical courses and histories were characteristic. They suffered from intractable wheezing in repeated severe attacks, frequently requiring hospitalization. They reacted poorly or not at all to the usual management with elimination of offending allergens, hyposensitization, and antibiotic therapy.

The vital capacities were determined during the period prior to Marisone, cortisone, and ACTH therapy. These determinations were recorded as controls. The convenient Buhl Precision Pocket-Size Spirometer approved by the Council on Physical Medicine and Rehabilitation,¹¹ was used instead of timed spirometric recordings of maximum breathing capacities. Readings were taken with the patients in a standing position at approximately the same time of day at intervals of three to seven days. The maximum volume recorded was that noted after three consecutive

STEROID COMPLEX IN ASTHMA—JAROS AND SPIELMAN

trials. Predicted vital capacities were determined from a standard table accompanying the above instrument.

In order to determine the maximum functional vital capacity of these patients during the control period, a bronchodilator drug was given (0.5 cc epinephrine hydrochloride 1:1000 or Butanephrine solution subcutaneously). These values gave some additional evidence as to the extent of existing pulmonary interstitial fibrosis and an index of the individual's capacity for maximum ventilation in the absence of bronchospasm.

The patients, all ambulatory, were then placed on steroid therapy, being seen at intervals of one to seven days, the observations being continuous for periods as long as 250 days at the time of this report. The group comprised seven males and seven females, their ages ranging from ten to fifty-four years. Unfortunately, the six females of the group of private patients in whom it was hoped comparisons of the effectiveness of ACTH or cortisone and Marisone could be made had to be dropped from this study both because of incomplete co-operation as well as the high cost of the parenteral preparations. However, of this latter group, it was noted that the vital capacity increased significantly after a few days of ACTH or cortisone therapy but rapidly fell upon cessation of treatment. Several of these patients prematurely and voluntarily stopped Marisone therapy because the response to it was much slower than to the other corticoids. The period of observation of this group was less than one month, while the minimum period of the remaining group reported here was eighty-three days and represents those individuals that were initiated and continued on Marisone alone.

Routine urinalyses, complete blood counts with differential counts, total eosinophil counts, and blood pressure readings were done at intervals, while vital pulmonary capacities were recorded once or twice a week. It was discovered that the eosinophil counts seen in blood smears sufficiently paralleled the total eosinophil counts, and the former are therefore presented in this paper. Even though the eosinophil counts are acknowledged to be a very reliable index of clinical responses, they are indicated herein simply as another objective and easily reproduced laboratory procedure in the follow-up of these patients.

The oral dosage of Marisone varied, but the majority of the patients received 400 to 600 mg (2 to 3 capsules) daily. In view of the doses used in the arthritis regimen, one patient in this group was given 1.0 to 2.0 gm in divided doses throughout the day. Subsequent patients not reported herein have been placed on the latter dosage schedule. At various intervals, placebo capsules, which were identical in color and size with the true product, were used.

RESULTS

All patients noted subjective improvement within the first week of treatment, although the objective signs were not significantly changed for three

to four weeks. Vital capacities gradually increased and soon exceeded the levels previously attained following treatment with broncho-dilating agents. In the course of continued therapy, further increases were seen in the majority of the patients so that the predicted capacities were often attained and occasionally surpassed.

Although patients experienced an increase in the sense of well-being and were markedly improved while taking Marisone, other attacks of asthma were not prevented when precipitated by a number of factors. These attacks, however, when they did occur were considerably milder in severity and were of much shorter duration than usual.

In most instances eosinophil levels fell as improvement was noted. This response is similar to that reported after ACTH or cortisone.^{10,20} Eosinophil levels rose with an exacerbation of the disease or with discontinuation of therapy.

CASE REPORTS

Case 1.—Patient L. D. (Fig. 1), a ten-year-old boy, had had recurrent, frequent severe attacks of bronchial asthma since two years of age which did not respond to hyposensitization. He had perennial nasal obstruction, rhinitis, and an abundant post-nasal purulent discharge secondary to a chronic pan-sinusitis which was easily activated by a propensity to develop frequent upper respiratory and generalized infections. A beneficial response was obtained with 200 mg Marisone per day with an increase in vital capacity; but after a moderately severe attack on the twenty-fifth day, the dosage was raised to 400 mg. There was a marked improvement which was interrupted by a severe furunculosis and coryza. It is to be noted that the increased response in vital capacity volume to epinephrine was greater than during the control period. This responsiveness to epinephrine became even greater as Marisone was continued. After another bout of illness similar to that above, Marisone prepared by a different process was used (cross-hatched area), which induced a prompt remission of the disease, with the vital capacity reaching the predicted level. On the substitution of a placebo there was a quick relapse without any signs of an infection. Improvement again promptly followed Marisone dosage.

Case 2.—Patient A. E. (Fig. 2), a twenty-four-year-old man, had had severe recurrent bouts of bronchial asthma since eleven years of age, concurrently with marked nasal obstruction, rhinitis, and profuse, purulent postnasal discharge from a chronic pan-sinusitis. He also suffered from hay fever each fall. Hyposensitization to dust and ragweed provided no relief. On 200 mg of Marisone there was a prompt remission of subjective complaints and an increase in pulmonary vital capacities so that by the seventeenth day he had reached his predicted capacity. After forty-eight days of therapy there were only two minor attacks, precipitated by coryza. Eosinophil levels fell to normal and did not rise until he discontinued therapy voluntarily. At this time the vital capacity fell with a mild attack. Subsequent intermittent dosages of Marisone were also followed by an increase in vital capacity. He was feeling so well that it was decided to discontinue therapy indefinitely. He has continued to be free of asthma and in spite of mild hay fever attacks has maintained a pulmonary vital capacity at a level previously attained only after epinephrine.

Case 3.—Patient J. E. (Fig. 3), a twenty-eight-year-old man, had had severe recurrent bronchial asthma perennially with severe nasal obstruction and rhinitis since

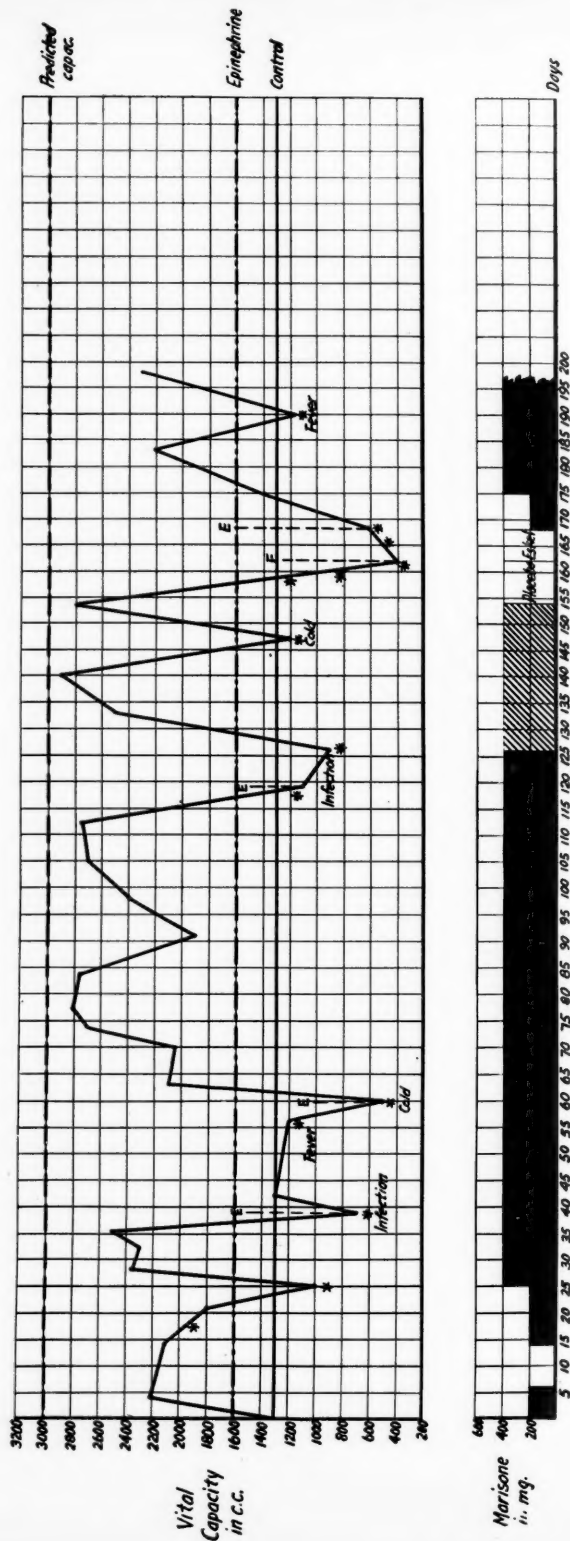


Fig. 1. Patient L. D., ten-year-old boy. Bronchial asthma and vasomotor rhinitis of eight years' duration. Previous treatment: dust, T.T.V. —no relief.

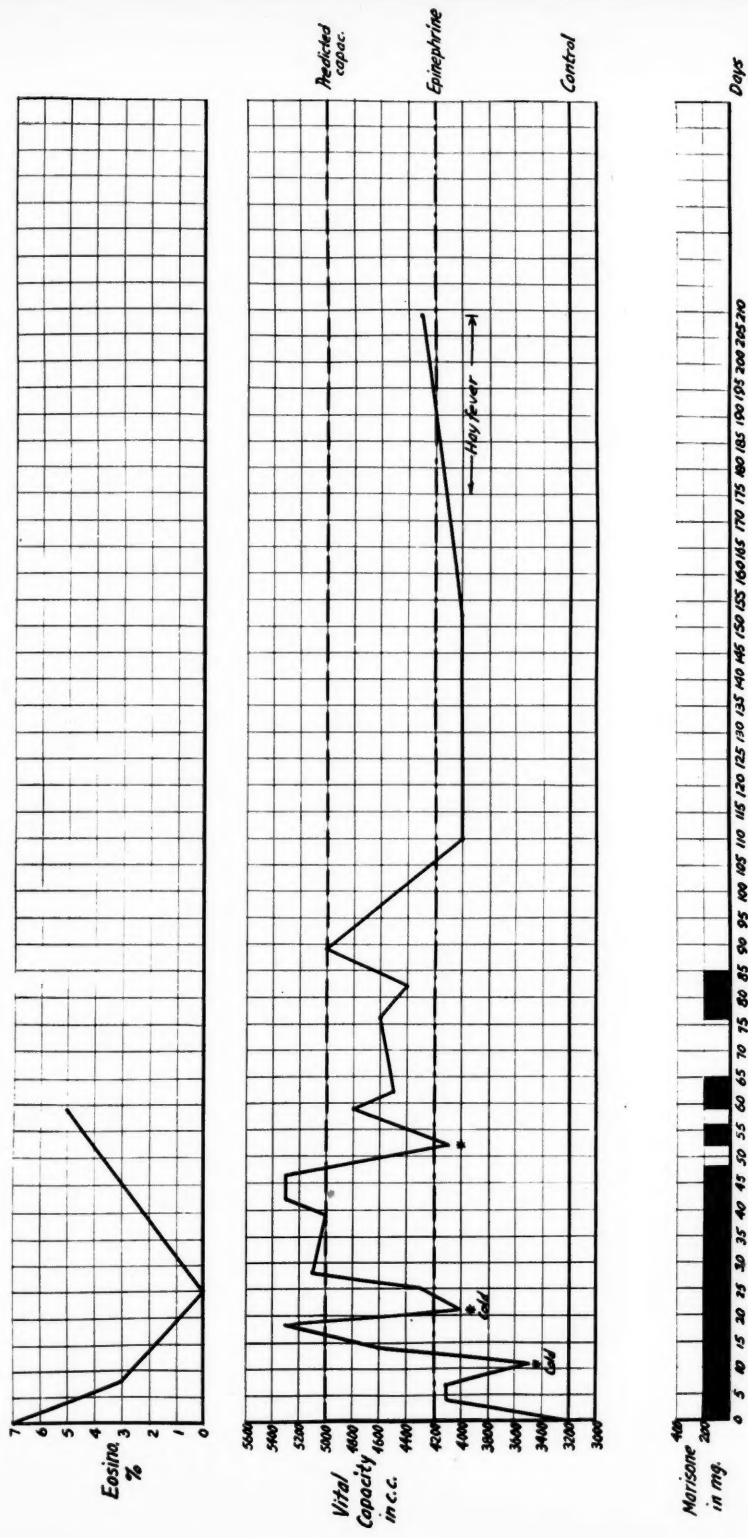


Fig. 2. Patient A. E., twenty-four-year-old man. Bronchial asthma of thirteen years' duration, with pollenosis, vasomotor rhinitis and sinusitis. Previous treatment: dust, ragweed—no relief. (*) Asthma attack.

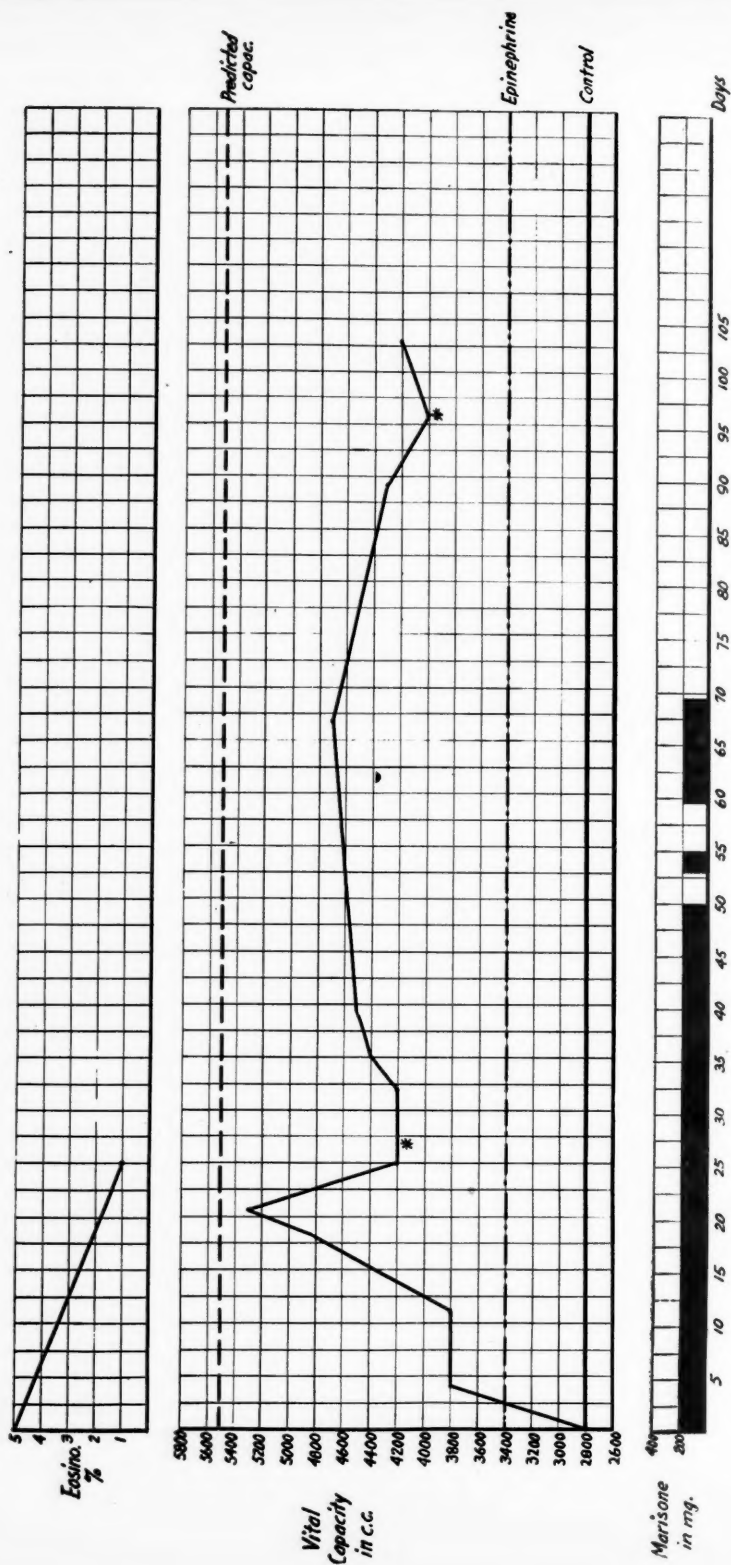


Fig. 3. Patient J. E., twenty-eight-year-old man. Bronchial asthma with vasomotor rhinitis of twelve years' duration. Previous treatment: dust, T.V.—fair relief. (*) Asthma attack.

STEROID COMPLEX IN ASTHMA—JAROS AND SPIELMAN

sixteen years of age. Only fair relief was obtained with hyposensitization. On institution of 200 mg Marisone there was a prompt subjective improvement paralleled by a marked increase in pulmonary vital capacity and fall in eosinophil levels. His ventilatory capabilities reached the predicted capacity, but this was lowered by an upper respiratory infection which produced a mild attack of asthma. Since then, and in spite of discontinuing Marisone, he has maintained pulmonary capacities at a level considerably better than those attained with epinephrine and has had no asthma attacks, except for a slight one precipitated by hay fever.

Case 4.—Patient A. P. (Fig. 4), a fifty-one-year-old man, had had recurrent severe bouts of bronchial asthma for fifteen years which, along with several attacks of pneumonia, had resulted in a moderate degree of bronchiectasis and emphysema. For many years he had had a gastric peptic ulcer which occasioned a gastric resection, gastroenterostomy, and three subsequent surgical procedures to resect adhesions causing intestinal obstructions. In addition, there was a marked posterior urethral stricture which was periodically dilated but, on occasion, would cause a retrograde pyelonephritis. During the past ten years he developed vasomotor rhinitis and hay fever. Hyposensitization provided only poor relief. This patient was given 1.0 gm of Marisone initially. Even though a virus bronchopneumonia developed, he was not very ill and the asthma was moderate. One day he voluntarily took an additional 400 mg, which made him asymptomatic the next day. When he was seen, the vital capacity was almost at the level attained with a bronchodilator drug. Marisone was discontinued. A fall in ventilating capacity was promptly noted, and he was hospitalized for treatment of a marginal peptic ulcer. Marisone was started again, followed by marked objective and subjective improvement, which was progressive except for a short-lived, severe hay fever attack. At the end of fifty-four continuous days of therapy, the vital capacity had exceeded predicted levels. He agreed to see how he would get along without Marisone. He did well, in spite of some hay fever, for thirty-three days. Therapy was given to prevent a marked fall in vital capacity. Although he experienced a pyelonephritis with marked fever and pain, there was no dramatic fall in vital capacity. Again on cessation of therapy he developed asthma along with an acute intestinal obstruction. Another course with the modified formula (cross-hatched area) produced improvement, and he had only one attack of asthma during a postoperative bronchopneumonia. Dosage was increased to 2.0 gm daily, followed by a prompt remission of his pulmonary symptoms. During therapy eosinophilia was below control levels.

Case 5.—Patient J. M. (Fig. 5), a forty-eight-year-old man, had had severe recurrent bronchial asthma for seven years in addition to a long-standing hypertensive heart disease. No relief was obtained from hyposensitization and nonspecific measures. Epinephrine was not given because of his cardiac status. Marisone therapy at 200 to 400 mg provided a sense of well-being and no asthma except slight attacks during a bout of pleurisy and when medication was stopped. Although the average vital capacity during Marisone therapy was better than without the drug, the average vital capacity over the entire period of observation fell 2.46 per cent and was coincident with the increased severity of his myocardial failure. During Marisone therapy there were no significant changes in blood pressure. The eosinophil count fell while on Marisone.

Case 6.—Patient F. L. (Fig. 6), a fifty-four-year-old man, had severe recurrent attacks of bronchial asthma from which previous immunologic treatment gave no relief. He had a marked degree of pulmonary fibrosis and emphysema secondary to an arrested pulmonary tuberculosis. A course of therapy with Marisone, 200 to

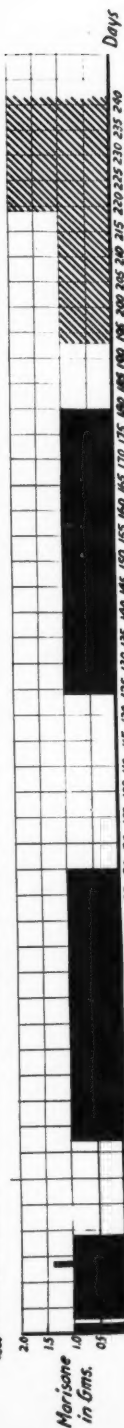
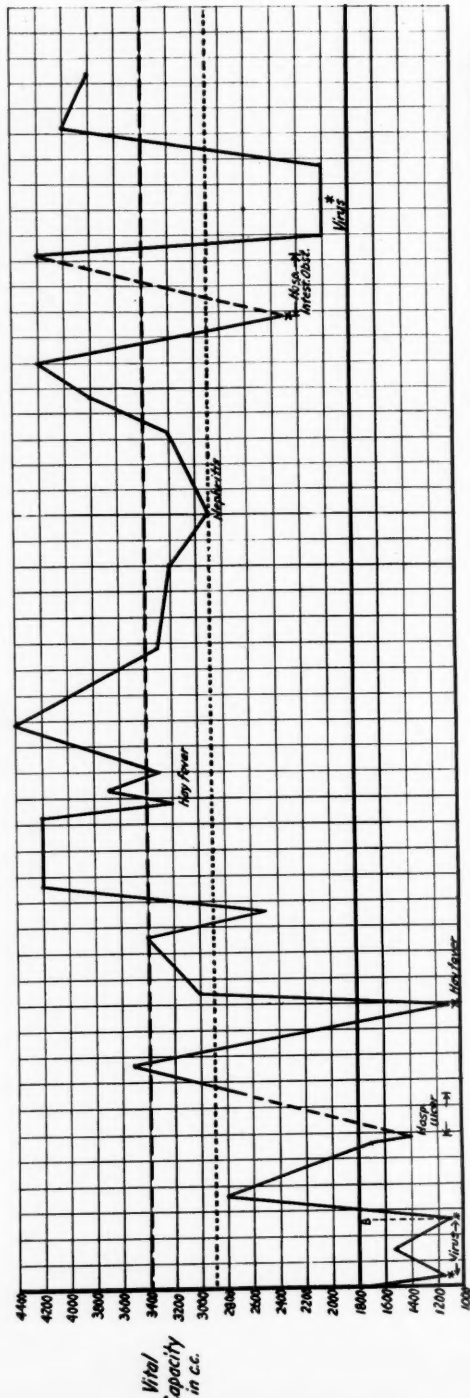
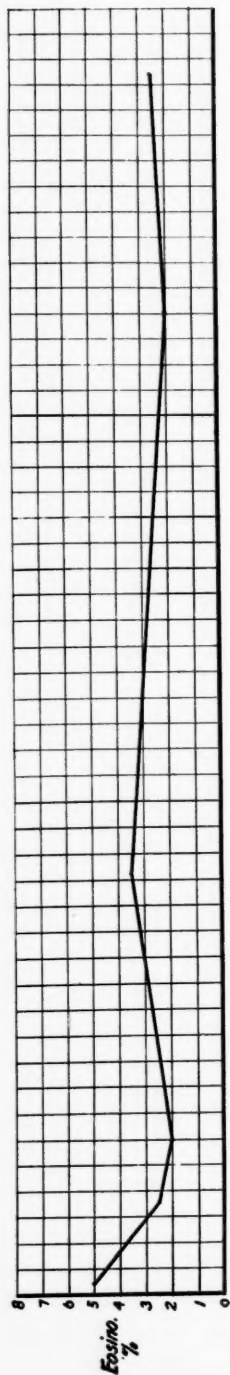
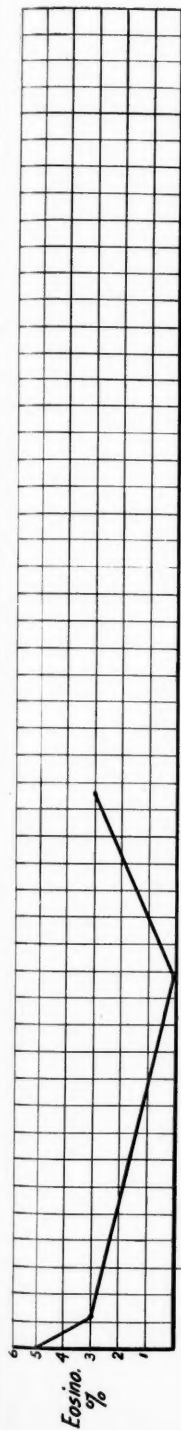
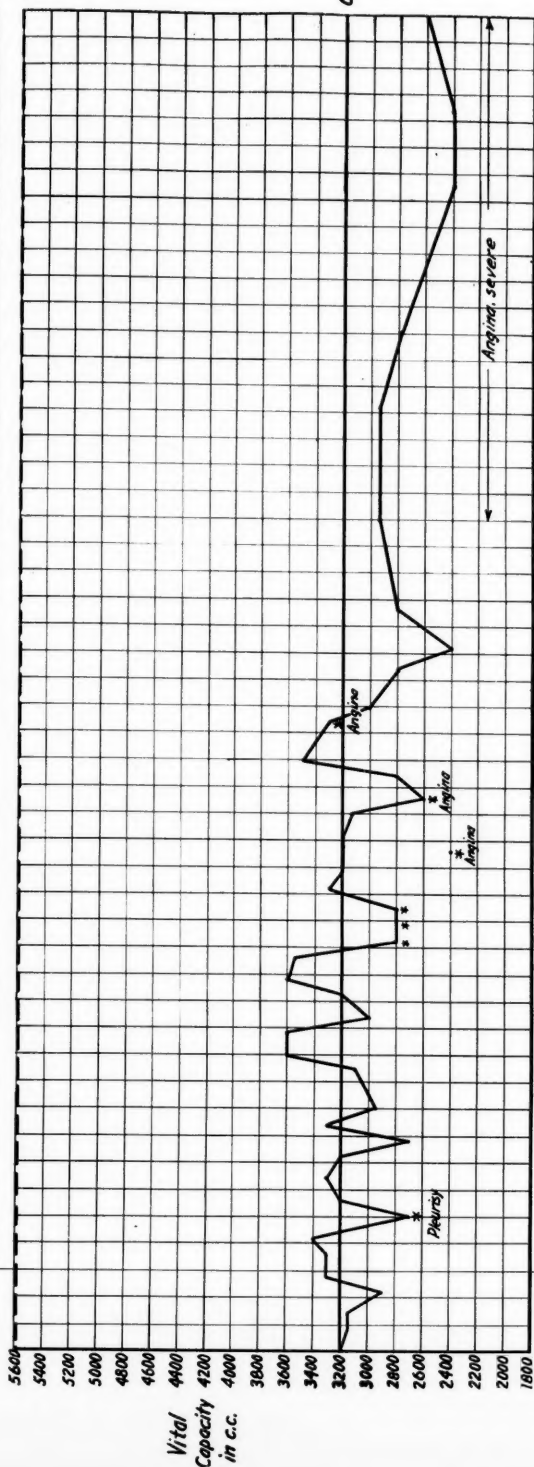


Fig. 4. Patient A. P., fifty-one-year-old man. Bronchial asthma of fifteen years' duration, with bronchiectasis, emphysema and peptic ulcer. Previous treatment: dust, pollens—poor relief. (*) Asthma attack.

Fig. 4. Patient A. P., fifty-one-year-old man. Bronchial asthma of fifteen years' duration, with bronchiectasis, emphysema and helpful relief. Previous treatment: dust, pollens—poor relief. (*) Asthma attack.



Predict apnoe



Control

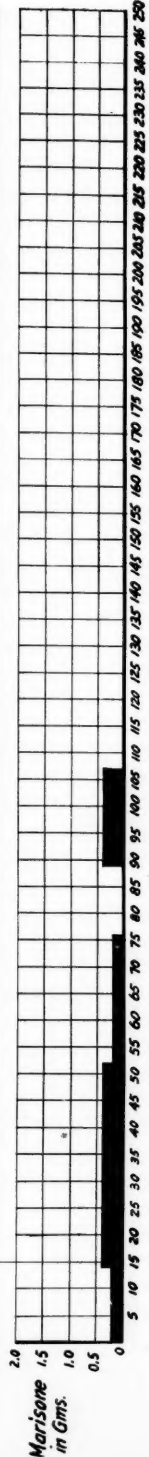


Fig. 5. Patient J. M., forty-eight-year-old man. Bronchial asthma of seven years' duration, with hypertensive heart disease. Previous treatment: dust, T.T.V.—no relief. (*) Asthma attack.

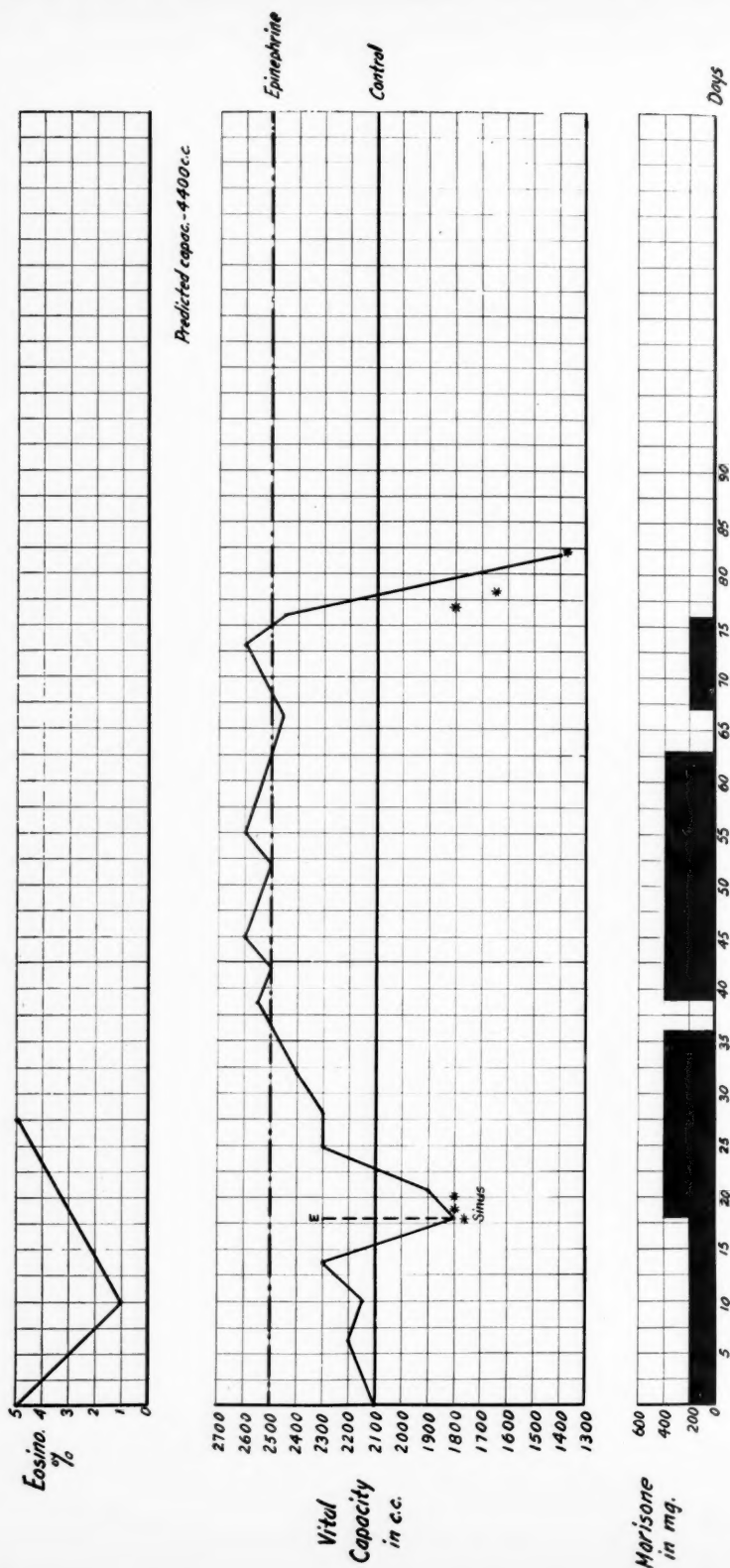


Fig. 6. Patient F. L., fifty-four-year-old man. Bronchial asthma of three years' duration, with bronchiectasis, emphysema, sinusitis and healed pulmonary tuberculosis. Previous treatment: T.T.V.—no relief. (*) Asthma attack.

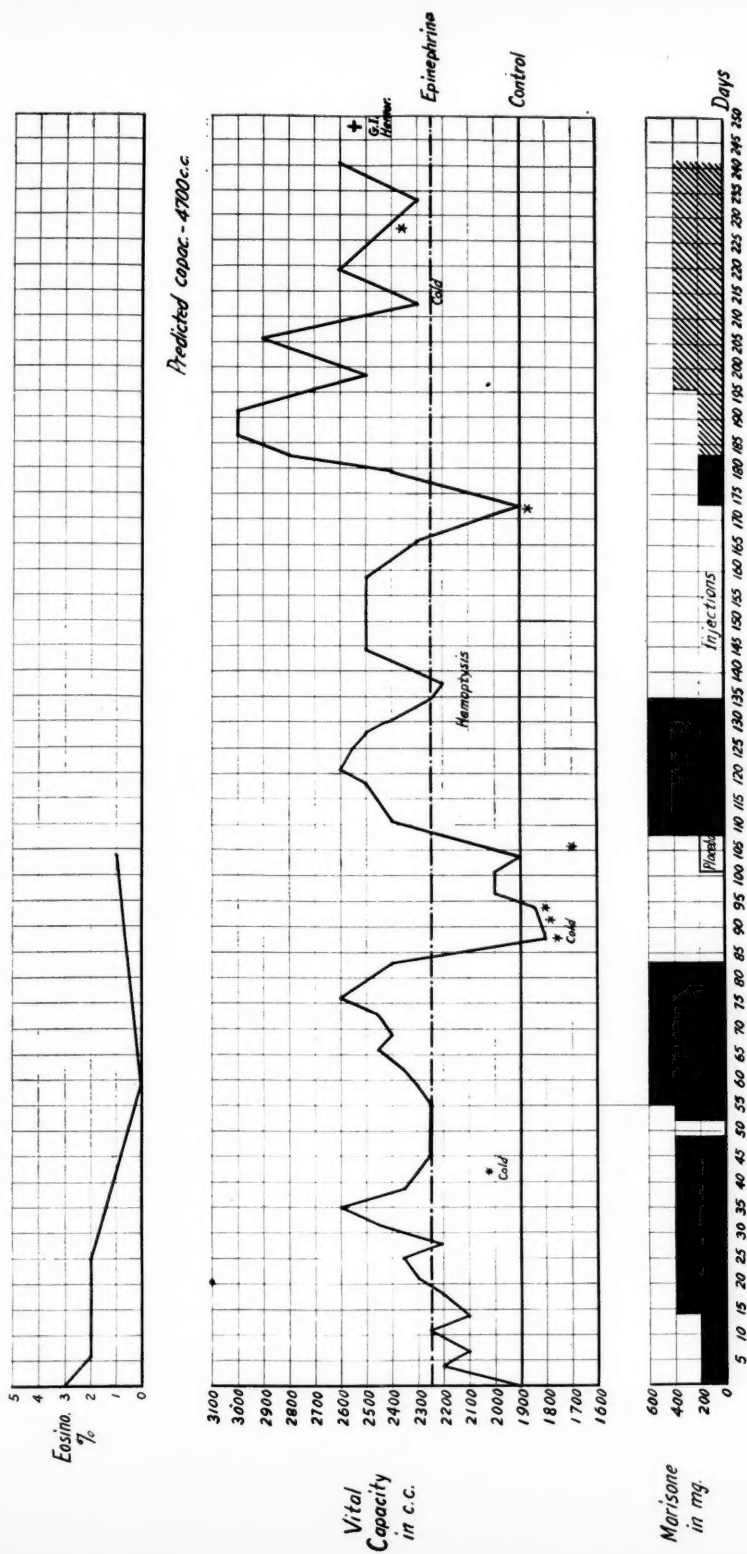


Fig. 7. Patient S. C., forty-nine-year-old man. Bronchial asthma of five months' duration, with emphysema, alcoholism and peptic ulcer. Previous treatment: symptomatic, dust, T.T.V.—poor relief. (*) Asthma attack.

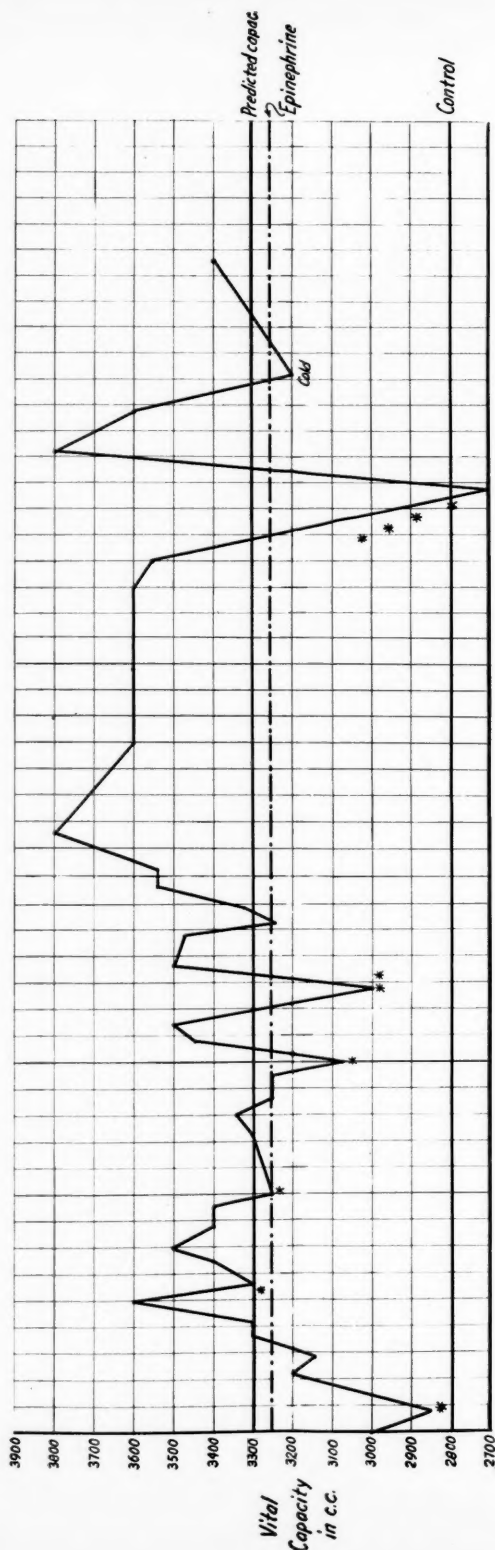
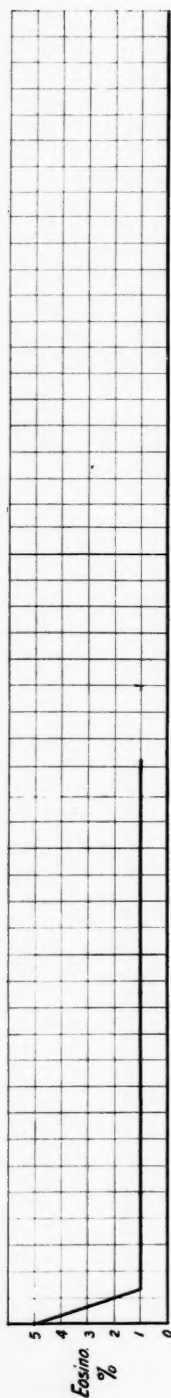


Fig. 8. Patient M. de L., thirty-one-year-old woman. Bronchial asthma of seventeen years' duration, with vasomotor rhinitis and sinusitis. Previous treatment: dust, T.T.V.—moderate relief. (*) Asthma attack.

STEROID COMPLEX IN ASTHMA—JAROS AND SPIELMAN

TABLE I

Patient	Vital capacity in c.c.					% aver. change from control
	Predicted	Epinephrine	Control	Marisone av. response	Marisone max. response	
L.D.	3000	1800	1300	1845	2900	+41.9
A.E.	5000	4200	3200	4483	5300	+40.1
J.E.	5500	3400	2800	4109	5300	+46.8
A.P.	3400	2900	1800	2843	4400	+58.0
J.M.	5600		3200	3121	3600	-2.46
F.L.	4400	2500	2100	2268	2600	+8.00
S.C.	4700	2250	1900	2352	3000	+23.8
M.dL.	3300	3250	2800	3360	3800	+20.0

400 mg, provided symptomatic relief and a gradual increase in vital capacity at a level previously attained only with epinephrine. During an attack of acute sinusitis with asthma, the response to epinephrine was increased over the control period. A prompt relapse occurred on the cessation of therapy.

Case 7.—Patient S. C. (Fig. 7), a forty-nine-year-old man, complained of recurrent severe bouts of bronchial asthma for five months, although he exhibited marked pulmonary emphysema. He had been a severe alcoholic for many years and had a gastric peptic ulcer. On Marisone therapy he improved progressively as the dosage was raised from 200 to 600 mg per day. An upper respiratory infection did not precipitate asthma. The eosinophil count fell to normal. After therapy was stopped, a mild coryza precipitated several severe attacks of asthma. Treatment with a placebo showed no improvement. Restitution of Marisone quickly raised the vital capacity again to exceed levels attained only with epinephrine. Discontinuance of Marisone was occasioned by a complaint of hemoptysis of unknown origin. Vital capacity reading began to fall after several weeks. Prompt improvement followed Marisone, again using both forms of the drug. This status was maintained until the patient was last seen. It was learned subsequently that he died from a massive gastrointestinal hemorrhage.

Case 8.—Patient M. de L. (Fig. 8), a thirty-one-year-old woman, had had severe recurrent bronchial asthma since fourteen years of age, along with perennial nasal obstruction, rhinitis, sneezing, and recurrent attacks of acute sinusitis. Previous allergic management had provided only moderate relief. A regimen of Marisone, 200 mg a day, provided almost dramatic relief after a week, with a marked increase in pulmonary vital capacity exceeding even predicted levels. Subsequent attacks were minor and nondisabling. After seventy-five days of therapy beneficial effects were maintained for three months without the drug. When therapy was started again, a marked response was observed which persisted.

A summary of the results is presented in Table I.

STEROID COMPLEX IN ASTHMA—JAROS AND SPIELMAN

The percentage change from the control studies represents the average of all vital capacity readings taken during the entire period of observation after the control values were obtained. The intervals in which Marisone was temporarily discontinued are included. Statistical treatment of the data was done; however, in view of the large number of observations over a long period of time, significant values are obtained simply by comparing the average vital capacity values before and after treatment.

Skin testing, using the scratch technique, was done on a group of five patients. It is apparent that Marisone does not suppress skin reaginic activity. No quantitative difference in positive skin reactions could be seen when elicited before and after Marisone dosages of 1.0 gm. Since Marisone is derived from an animal source, it was used as an allergen to skin test two patients known to be sensitive to horse serum and horse dander. Only questionable reactions were seen.

Marisone was well tolerated, producing no undesirable side effects. There were no appreciable gastrointestinal disturbances. There were no toxic effects seen that might manifest themselves through the examination of the peripheral blood or urine. There was no significant effect on blood pressure or the pulse rate.

DISCUSSION

Clinical investigation of Marisone, a natural steroid complex, shows it to be useful in helping to control severe bronchial asthma in patients who previously required repeated hospitalizations. It is apparently safe, non-toxic, and well tolerated in large doses. The mode of action in producing beneficial results is not readily apparent. The compound does seem to have a profound effect in causing a suppression of progressive pulmonary fibrosis, as indicated by marked increases in vital capacities considerably in excess of levels seen during the control period and following the use of bronchodilator drugs prior to Marisone therapy. This agent may contain steroids which can act as precursors or direct replacements for enzyme-activating steroids which cause relief of persistent residual bronchospasm and/or which increase the elasticity of fibrous scar tissue by inhibiting the inflammatory response.

The fall in eosinophil cells in the peripheral blood, the increased responsiveness to epinephrine, and the lack of inhibition of skin reagins resembles that seen following administration of other adrenal corticoids.

The progressive increase in pulmonary vital capacities is gradual, with definite improvement seen by the third or fourth week of continuous treatment. Upon the cessation of therapy the clinical benefits have a carry-over effect that is approximately equivalent to the duration of the therapy; i.e., relapses occur within a few days in those patients with short courses of therapy; in those on Marisone for several months, remissions vary from weeks to months. Prolonged continuous dosage regimens are nontoxic and well tolerated (patient L. D. for 140 days). In adults, doses of 2.0 gm

STEROID COMPLEX IN ASTHMA—JAROS AND SPIELMAN

should be offered for the first three or four weeks, then reduced to a lower level sufficient to maintain beneficial effects. Occasionally, patients on high doses may complain of a turgescence of the breasts. In such cases, doses are reduced or therapy discontinued for a short period.

CONCLUSIONS

1. Marisone, a natural steroid complex, substantially estrogen-free, derived from pregnant mares' urine, is useful in attaining increased pulmonary vital capacities in patients with severe, intractable bronchial asthma. It does not prevent further attacks but mitigates them so that they are less frequent, severe, and prolonged.

2. This compound is safe, nontoxic, and well tolerated for prolonged periods of administration.

3. The effect of Marisone on eosinophilia, and other peripheral actions, resembles those caused by some of the adrenal corticoids.

4. An explanation of its possible mode of action is presented—that this compound stimulates the availability of enzyme adrenocorticoids.

5. Clinical experience indicates that Marisone is a useful adjuvant type of therapy. Its use will increase maximum pulmonary ventilatory capacities when given along with the usual methods of allergic management. The clinical results appear encouraging and to warrant further investigation.

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COMBINED ALLERGIC AND PSYCHOSOMATIC TREATMENT OF BRONCHIAL ASTHMA

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WHENEVER we discuss the *cause* of any allergic manifestation, we leave the realm of medicine (or to give it its classical name, *physic*) to enter the realm of metaphysic. In this sense, the word "cause" has at least eight separate meanings. Philosophically, it is the sum total of the conditions, positive or negative, taken together: the whole of the contingencies of every description which, being realized, the consequence invariably follows (J. S. Mill). Its subsidiary meanings vary semantically. A car overturns while rounding a curve. To the driver, the cause is his excessive speed. To the road engineer, the cause is insufficient banking of the road. To the manufacturer, it is the center of gravity of the car which is not sufficiently low.

When we have discussed all the operative causes of the patient's allergic response—namely, his heredity, his sensitivity, his shock-organ inferiority, his exposure to the causative allergens, the effect of superimposed infection, and the trigger mechanisms, any of which may, at any time, appear to act as a primary cause—we are still faced with a number of possible, usually secondary, causes, namely, those neurological and psychological in nature. The present paper will emphasize the secondary or psychosomatic causation, although this may, on occasion, appear—as we shall see—as the sole cause of, or better still, the reason for, the patient's wheezing.

Neurological and psychological causes must be listed separately, because wheezing may be due to the conditioned reflexes, as well as to suggestion and emotion, the latter due directly or indirectly to mechanisms of adjustment.

The conditioned reflex type of response is, in its simpler form, easily recognized. The patient who wheezes at the sight of an artificial rose or a stuffed cat has long been the target of the comedian. In more subtle form, the continuation of symptoms, when the causative allergen has been removed, is often due to conditioned reflex effects as in the return to an environment in which, in the past, asthma has invariably occurred. We often change these, in effect and externally, when we alter the incident circumstances, namely, the furniture, the room, the house or the part of the city, or when we move the patient to other rooms, houses or cities free of association with his wheezing.

Internally, the same results follow direct counter-suggestion, or indirect counter-suggestion, as by injection treatment or by medication, any or all of which may carry the patient through the same environment and its

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emotional components, but with blocked reflex mechanisms. A patient sensitive to feathers, and free of such conditioned reflex responses, will wheeze when sleeping on a feather pillow. We can balance this with the patient who is free of wheezing when his pillow has been covered and wheezes with it uncovered, and yet who, when he goes to a hospital for concomitant surgery and sleeps on uncovered pillows and mattresses and in a new environment containing allergens to which he gives no thought, remains free of wheezing. He is symptom-free, that is, until his exposure is brought to his attention, following which he presents symptoms. Such oversimplifications are, however, not always the complete explanation for such behavior, although the sedative effects of Benadryl or the personality changes due to ACTH injection treatment may be helping the patient above and beyond their specific medical properties.

Emotional causes, when immediate and acute, are easily recognizable by both the patient and the physician. A shock, a near-accident, a death will as often precipitate attacks as they will just as frequently terminate them. In each case, the causal relationship can be given its proper place in the over-all picture. When less obvious, as in mild manic-depressive patients, in whose depressed phase exacerbations most often occur, such relationships are not always recognized as psychic in nature. In women, exacerbation during the third and fourth weeks of the menstrual cycle may be due to such psychic causes rather than to endocrine imbalance, although both may be present and interrelated. In this group belong the businessman under tension, the student fretting over impending examinations, as well as the young woman, married or single, hopeful or fearful of pregnancy.

When we go beyond the conditioned reflexes and mood swings, we touch upon the true psychosomatic mechanisms, those in which, although allergy is present, the patient's wheezing is due, in part, to his lack of adjustment to his psychological environment, or to reality. Fortunately for us, as physicians, when a patient fails to solve his psychological problems at the emotional and intellectual level of the mature adult, he has a limited number of choices among the reaction mechanisms available to him. Such defense mechanisms are not always recognized by the patient (or for that matter, by the physician) for what they really are. Successful treatment resides in the concept that, knowingly or willfully, they are a matter of choice. However much we may dislike to face this fact, and facing it is for the physician, as well, a part of his maturing process, we, as human beings, do have a choice. There is that one moment, however brief, in which we deliberately choose to act so as to solve our problem, or to reject its almost always obvious solution.

For example, when faced with a spoken insult—in other words, a rejection—and granted that it is truly possible to insult us, we can choose our response. However hair-triggered our tempers, we can, at the adult level, pause, smile, and with utter disbelief, ask that the words be repeated, or we

BRONCHIAL ASTHMA—BROWN

can, at the infantile level, act by regressing into anger, negativism or aggression, none of which solve the problem. We can, of course, regress purposefully and with as much emotion as the situation requires to prevent its recurrence. We then know what we are doing, and why, and the experience in which we play the role of an actor leaves no psychological scars.

In allergic patients such responses, when neurotic and leading to psychosomatic symptoms, are the usual ones. The patient responds with wheezing to situational problems which he does not solve but from which he takes flight into states of regression, anxiety, guilt, and self-punishment, introjection, displacement, and passive conflict. Rarely, his manifestation of escape from reality may take the form of narcissism or phantasy. On the other hand, the borderline allergic patient may retreat into those mechanisms of adjustment which act to pull him out of an asthmatic attack when wheezing is incompatible with his response, as when he chooses aggression, active conflict, projection, sublimation, compensation, and reaction formation. Rationalization may, on some occasions, lead him into exacerbation, or remission, in accordance with his previous successful evasion of his problem with either state.

When the type of reaction becomes as fixed and as compulsive as a conditioned reflex, deep analysis may be necessary. It frequently uncovers the series of incidents which, repressed at the infantile level, nevertheless evoke the response seen in the neurotic adult. The patient is like a phonograph record. Each incident is regarded as a phonograph on which his record can be played. Failures of analysis occur, of course, when the patient fails in his attempts to uncover the repressed causative constellation. Sometimes when it is uncovered and externalized, we discover that this is not enough. Insight and acting out are not always the answer. In some cases, the patient recognizes the neurotic reasons for his abnormal behavior, but his responses remain the same. He knows why he responds to a situation by wheezing, but continues to wheeze. To become mature at the problem-solving level is hard work, day in and day out, and most of us are incapable of the sustained effort it takes, both to grow up and to continue grown up.

The best example is the story of one of Freud's patients, a neurotic young woman who had completed (if that is the word) a successful analysis. When she was asked how she felt, she answered, "Fine, but of what conceivable use is it to be a completely adjusted person in a completely maladjusted world?"

Naturally enough, we do not and cannot completely adjust everybody to everything. In our patients who are, beyond cavil, allergic, and beyond argument, neurotic, we must combine the functions of internists, allergists, and psychiatrists. We do this by recognizing the causative factors in both fields. We accept as a working hypothesis the slogan that no one wheezes excepting for a cause and for a reason. We eliminate the direct cause, we

immunize when we cannot eliminate, we medicate when elimination or immunization are impossible or incomplete. We operate when necessary. When all this has been done, we stop looking for causes and search for reasons. The recurrent pattern of the patient's responses gives us our cues.

Let it be clearly understood that we do not always succeed. We are sometimes in the position of Allport, who said to a patient, "Madam, the problem is not that you have an inferiority complex. The truth is that you are really inferior."

A brief example of such mechanisms will be sufficient. Since regression is the most important of the mechanisms of adjustment chosen by our patients, we can use this as a scaffold for understanding other types of flight from reality.

The patient whose attacks occur with simple regression, namely, with the desire for dependence and the care given by parents, family, or friends, or occasionally by nurses or doctors, is familiar to every physician. Such regression may be due to conflict with the sibling, or with the parent of the opposite sex, to a feeling of rejection, or sometimes, in very allergic individuals, to a simple lack of energy, without which the patient can neither face his problems nor realistically solve them. Senile patients, as well as children, can regress to negativism, namely, to a more childish level of response, and in some cases, to slovenliness of body and person at the infantile self-soiling level of development. Many of us forget almost completely how we responded at this stage of our growth. The neurotic individual may forget mentally, but he has remembered in body response patterns. In these patterns, asthma may be the psychological equivalent of childlike weeping, as in one of my patients who reacted to her father's death with wheezing, but with no tears. When the tears came, the wheezing ceased. Wheezing as an equivalent for tears has been noted by many observers.

Situational regression is also familiar to most of us, since it occurs in one form when in a youngster, the parents are present. The patient's problem is resolved by regression into active conflict, or else into negativism which is directed against every adult present. Removing the parents, or removing the child to another situation, changes and eliminates the regression. The patient then no longer refuses to be examined or to be tested.

Regression into asthma also occurs in those patients who, with mild attacks, seek their beds, indulge in oral or auto-erotic practices such as over-eating, nail-biting or thumb-sucking, or, who become asthmatic when their positions are threatened, as with the arrival of a new baby, or in adults, with the promotion over their heads of one previously inferior.

One of my patients, who as counter girl in the office of a small country newspaper, and who had been free of wheezing for years, had a recurrence of her symptoms when the publisher's daughter was given a summer job beside her. The daughter, although inferior in knowledge and experience,

had more authority and influence. The situational regression into wheezing was explained to the patient, who took a vacation and returned to her job when the publisher's daughter returned to college. In the ten years which have intervened, there has been no recurrence of the asthmatic attacks.

The asthmatic patient who whines, fusses, or has to be coaxed to take his medicine or treatment should be suspected of regression. It should also be suspected in those in whom asthma ceases when the patient indulges in any activity carried on at a lower, and therefore more satisfactory, level of maturity, as in men, while playing games or attending alumni meetings; and in women, on the occasions when they go home to mother, or in both when there is the psychological equivalent, as when a patient's asthma ceases when he breaks a leg or when he is free of responsibility, as on a vacation.

In one of our patients regression by identity and by conflict were both present. The patient, who was herself free of asthma, brought her daughter to the clinic. Sensitivities to feathers, house dust, and cat dander were discovered to be present and corroborated by skin tests and clinical history. The child's father was overseas, and the child and her mother lived with the child's grandmother, who had two cats. She, disliking her son-in-law and his child, namely, her grandchild and our patient, refused to do anything about the animals. A month later the child's mother came in with a continuous wheeze, moderately severe in degree. A physical examination, the usual laboratory studies, and skin tests were all negative. During the psychiatric interview, the patient confessed openly that her wheezing was an attempt to get her mother (the child's grandmother) to eliminate the cats, since she and her daughter were both affected by them. The patient refused medication since she was certain it would do no good, in other words, would not serve her purpose. When the cats were eliminated, both mother and daughter continued to live happily with the grandmother, both being free of symptoms.

Regression through narcissism may be suspected in a patient whose asthma ceases when, as a male, he dresses in a uniform for a parade, or when, as a female, is the better for a new hat, or in the case of one of my patients, the possession of a mink coat. She was well until her sister's husband bought his wife sables, an example of regression by rivalry.

The patient whose asthma is associated with what she thinks is the loss of her husband's love, is regressing into what Freud terms nostalgia. Other husbands and wives, unhappily married, use their asthma as a tool of aggression, only too often thinly disguised as a method of "getting even." In two of my patients, the wheezing was a manifestation of a true paranoia.

One of our patients illustrated to perfection the complex relationship of allergic, nonspecific, and psychosomatic factors. While taking his history it was discovered that he smoked forty to fifty cigarettes daily. The physician immediately capped his fountain pen and told him that there was no use going on, since this irritating factor in itself was sufficient to explain

BRONCHIAL ASTHMA—BROWN

the patient's cough and wheeze, and that no studies would be done until the effects of the smoking could be evaluated. The patient, who had been seen by four physicians previously, none of whom had asked him about smoking, accepted the physician's dictum and stopped smoking for a month, following which his cough and wheeze completely disappeared. At a review visit later, he volunteered the information that, although he was certain that his cessation of smoking had cleared his asthma, he was equally sure that it was not the irritation itself, because in his new-found state of health he felt so much less "guilty." He had always felt that he should not have smoked, but had never been given a sufficiently strong stimulus to stop smoking. He was himself certain that his sense of guilt in continuing to smoke was as much responsible for the asthma as the irritant nature of the smoking itself. The patient, the chief executive of a large engineering firm, international in its activity, after ten years of wheezing has been completely free of symptoms for two years, although subsequent skin tests showed him to give a large reaction to house dust and feathers. No dust precautions had been followed and no medicine taken during this intervening period of time.

In one of our patients, a very bright boy of ten, whose wheezing had driven his parents to distraction, a psychological cause was suspected. After the patient's parents had been sent away, the patient was assured that whatever he said would not be told to his parents. He was then asked, quite frankly, why he had been making such a damned nuisance of himself. To this he replied that if he didn't get to summer camp, he was going to make a greater nuisance of himself. He was assured that his confidence in the physician would not be broken, if with going to camp, he would be free of symptoms. His parents were told that he needed a summer in camp. Although he was typically allergic and required injection treatment for his sensitivities, he went through the summer free of symptoms, in part because he got what he wanted and in part because his pride would not permit him to let the physician down.

These are the minor manifestations of psychosomatic relationships. When major, the patient is no longer in the borderline group. The regression, when it shows itself as hysteria, as true manic-depressive psychosis, as schizophrenia, as hypochondria, paranoia, melancholia, or catatonia, belongs in the hands of a psychiatrist. At this level the patient has in a way solved his problem by other means and no longer needs his allergic responses. He is happy in his unhappiness, has succeeded in his escape, and no longer needs to wheeze, sneeze or itch. There are few asthmatic patients, indeed, in insane asylums.

Philosophers have often remarked on the intelligence of children and the stupidity of adults. In the practice of allergy, how rarely in children do we see the self-reliance and inner security of the emotionally stable? On the contrary, how often do we see the results of overanxious, dominat-

(Continued on Page 367)

TREATMENT OF CERTAIN DERMATOSES AS BACTERIAL ALLERGIES

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SUCCESSFUL treatment of certain skin conditions with mixed bacterial antigen plus antibody was described to The American College of Allergists in April, 1949.² Further experience, new clinical evidence, and corroboration of the principles involved, by various other workers, provide much more assurance that this method of treating psoriasis, pustular bacterids, eczema-dermatitis, and many erythematous and papular eruptions, is extremely valuable and will often improve and cure cases when the current standard treatments have failed. In one series of consecutive, unselected cases improvement occurred in twenty-eight of thirty cases of psoriasis, all of twenty cases of pustular psoriasis or bacterids, all of sixty-one cases of eczema-dermatitis, and twenty-nine of thirty cases of erythematous and papular rashes.

In the latter two groups if a contactant or ingested allergen can be found and avoided with resulting cure, treatment with bacterial antigen is unnecessary; but when improvement following avoidance of a known allergen is only partial, it often becomes complete under sensitized vaccine therapy. This may mean that of several causal factors bacterial antigen was one—possibly the major one.

In all types of cases the evidence is very conclusive. Where local applications have been used, this is no more than has to be done in order to relieve itching in many cases after *obvious* allergens have been avoided. However, the marked benefits observed cannot be credited to the local treatment employed for a number of reasons:

1. Areas where no local treatment was used often cleared as well as where it was used.
2. Improvement continued after local treatment stopped.
3. Sometimes after many years of continuous eruptions, response was prompt, even dramatic, following the vaccine.
4. Where good standard treatment had been employed without success by physicians, dermatologists, and allergists, for whose judgment and ability the author has every respect, cure often followed sensitized vaccine therapy.
5. In some cases no local treatment was used.
6. An exceptionally large number of patients mention that their rash *feels* different early in the course of treatment with sensitized vaccine.

The following seems to corroborate the theory and practice of this type of treatment:

Psoriasis.—Showing that psoriasis seems to be associated with disturbed production of steroid hormones, Reiss⁶ suggests that an infectious cause is highly probable. He thinks psoriasis is an allergic disease.³ Norrlind⁵ showed that psoriatic patients, compared with controls, gave a high degree of positive streptococci agglutination reactions. In his opinion, infections, especially of the respiratory tract, may promote the outbreak of psoriasis. On the author's suggestion, several general practitioners have cured cases of psoriasis by using the antigen-antibody combination.

Pustular Psoriasis.—In recent years it is being suggested that pustular psoriasis ought rather to be called bacterid,³ and that it is not likely to be cured unless a focus of infection is removed. Since publishing a report of twelve consecutive, unselected cases cured with sensitized vaccine,³ the writer has had eight other cases responding similarly. Two of these had some concurrent psoriasis. Similar results have been reported in a personal communication from Dr. Manuel Bloom of Houston, Texas.⁴

Eczema-Dermatitis.—Using patch and intracutaneous tests with autogenous vaccines on over 100 patients with eczema of unknown cause, as well as vaccines from other sources and control tests on other persons, Dr. Hans Storck,⁹ Zurich, Switzerland, found marked individual differences, which he thought indicated specific hypersensitivity. He thought bacteria might be the exclusive allergen or only one of several, and suggested the possibility of desensitizing or immunizing the skin. It seems to the author that for several years he has been doing what Dr. Storck suggested as a possibility.

Erythematous and Papular Eruptions.—A variety of erythematous and papular rashes have at least one feature in common: viz., the cause is not proven nor is treatment very satisfactory. With the use of sensitized vaccine in a variety of cases lasting from one week to forty years, some were benefited promptly and cured completely. Others seemed to be controlled, the rash flaring up somewhat when no vaccine was given for several weeks but disappearing under the vaccine therapy. Persistence in treatment finally cured most of these latter. Andrews et al¹ have shown that of seventy-eight patients who had pustular bacterid, eczema-dermatitis, pustular rosacea, or chronic urticaria, forty-five were cured permanently by removing foci of infection.

A few cases of lupus erythematosus and acne rosacea have been arrested by treatment with sensitized vaccine, and some of eczema of the ear canal and of severe pruritus ani have seemed to require such treatment in addition to local applications before they would clear up.

Pointing out that conditions responding to cortisone or ACTH are often also improved by so-called nonspecific, fever, and shock treatment, Selye⁷ suggests that the latter measures elicit a general adaptation syndrome,

especially an increase of ACTH and glucocorticoids. He thinks that a number of maladies depend upon a derangement in the pattern of corticoid secretion. May such derangement be due to circulating toxins? If so, to supply the missing hormone is useful symptomatic treatment, but to remove the depressing toxins would be more fundamental and curative. After working with sensitized vaccines for twenty-five years, and using them in certain skin diseases for about eight years, it seems to the writer that these products tend to influence the body's way of reacting to the presence of germs, the influence being always favorable. Whether or not complete recovery ensues perhaps depends upon whether or not the derangement of glandular activity is temporary and reversible or permanent and irreversible.

In vaccination of all kinds we can use attenuated or dead bacteria to deceive the body into organizing defences as though they were alive. Some of the resulting resistance is nonspecific. The combination of antibody and antigen makes it possible to safely administer twenty or more times as many dead bacteria as otherwise. Perhaps this is sufficient to stimulate enough anti-invader forces to satisfy "the brave skin" (as Sulzberger calls it) so that it need no longer dilate vessels, pour out serum, pile up scales, or send out an itching call for the hands to rub and scratch away a real or imagined contactant. In practice this often seems true!

Neither this paper nor the pictures accompanying it *prove* anything. They rather describe certain procedures concerning whose value doubt is not likely to linger in the mind of any fair-minded observer who will conscientiously begin treatment according to the following rather dogmatic rules and gradually develop his own technique based on his own experiences.

Product.—Serobacterins, manufactured by Sharp & Dohme, Inc., Philadelphia. Where sinusitis is suspected, *Haemophilus influenzae* "Serobacterin" Vaccine Mixed, No. 4750, a respiratory mixture, representing 7,000 million organisms per cc is first employed. If complete cure of the eruption does not occur, a course of Staphylo "Serobacterin" Vaccine Mixed, No. 4822 should be added. It is sometimes wise to combine the two products from the start. Where sinusitis is not suspected, the Staphylo "Serobacterin" Vaccine Mixed, representing 10,000 million organisms per cc (Staphylococcus, Streptococcus, Pneumococcus, *Escherichia coli*) is employed alone.

Administration.—*Subcutaneously*, not intramuscularly! Doses over 1 cc are best given one-half in each of two sites.

Intervals Between Doses.—Three days or more between smaller doses and five to seven days between larger ones. Do not give the same or a

DERMATOSES AS BACTERIAL ALLERGIES—BAIRD



Fig. 1. W. P. on April 29.

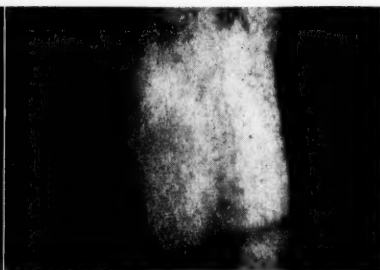


Fig. 2. W. P. on May 12.



Fig. 3. R. H. on July 27.



Fig. 4. R. H. on August 1.

larger dose after over one month, because many persons lose considerable immunity around that time.

Dosage.—The vast majority, including infants and children as well as adults, tolerate the following doses very well: 0.2 cc; 0.4 cc; 0.8 cc; 1.2 cc; 1.8 cc; 2.5 cc. It may be necessary to repeat the last dose several times at intervals of one to four weeks, and a few patients have to be given from 3 cc to 3.5 cc before securing maximum good results.

Local or general reactions are seldom severe and never serious. If severe, repeat the dose once or twice before proceeding to larger ones.

CASE REPORTS

W. P., forty-six years, male. He was seen on April 29, 1950. He had psoriasis of several years' duration on the upper anterior surface of his right leg with scales (Fig. 1). His nasal breathing was much blocked. He was given sensitized vaccine, nasal drops, and a simple soothing ointment. In one week the scale was gone and he was using ointment only once a day. The second picture taken on May 12 shows areas very pale and plainly healing (Fig. 2). By June 2 the condition showed further improvement, with some areas of skin approaching normal.

R. H., fifty-four years, male. Pimply spots on backs of his hands six weeks before developed into severe dermatitis with pustulation and crusting two weeks previous to first picture taken on July 27 (Fig. 3). Dressings by a general prac-

DERMATOSES AS BACTERIAL ALLERGIES—BAIRD



Fig. 5. Mrs. L. S. on May 27.



Fig. 6. Mrs. L. S. on June 5.



Fig. 7. J. C., initial condition.

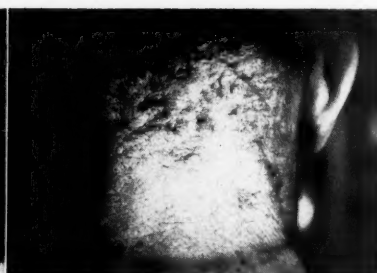


Fig. 8. J. C., after fifteen days of treatment.

itioner had produced very little relief. With ung. hydrarg. ammoniatum as a dressing, and a series of inoculations, there was marked improvement in two days. He said, "The fire has gone out of it." The second picture (Fig. 4) was taken five days after the first picture. The patient returned to work eighteen days after the first visit and was discharged as cured on the thirty-third day.

Mrs. L. S., twenty-three years. A picture taken on May 27 shows a condition which had lasted for one month (Fig. 5) and which this writer diagnosed as pustular bacterids. Some small spots were beginning to break out on the anterior part of the soles. The second picture (Fig. 6) shows progress nine days after the first, following three inoculations but *no* local treatment. When the condition later became somewhat itchy, she used a proprietary ointment which she had previously used without obvious relief. A month after second picture patient was discharged as cured.

J. C., sixty-three years, male. He had a weeping crusted dermatitis on the back of his neck (Fig. 7) following small pimples and boils three weeks previously. Sensitized vaccine and a soothing ointment gave great improvement in four days and almost complete cure in fifteen days, when the second picture was taken (Fig. 8).

E. C., twenty-two years, male. He had had infantile eczema when two to eighteen months old. For the last seven years he had had recurring attacks of a rash which became especially bad in November, 1949. Many ointments, x-ray, and ultraviolet

DERMATOSES AS BACTERIAL ALLERGIES—BAIRD

ray had been used. The condition was diagnosed by a dermatologist as recurrent atopic dermatitis. He was first seen on April 2, 1950. With soothing ointment, some sedative, and sensitized vaccine he was very much better in seventeen days and had completely normal skin in less than six weeks.

SUMMARY

Improvement and cure of large percentages of various dermatoses by treatment with bacterial antigen combined with antibody is reported, with several case reports and pictures to illustrate some of the spectacular cases. Some evidence from other workers seems to corroborate the theory that sensitivity to bacterial products is at least one cause of these conditions.

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A THEORY FOR ALLERGY AND EXPERIMENTAL EFFECTS OF ANTIHISTAMINES ON THE COMMON COLD

(Continued from Page 307)

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630 W. 168th Street.

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335

THE ALLERGIC AND NONALLERGIC CAUSES OF ECZEMATOUS HAND ERUPTIONS

I. Incidence

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IN the literature of the past decade there have been numerous reports on various types of vesicular and pustular eruptions of the hands. For instance, Rowe¹⁸ reported eighty cases in which he established food as the etiologic agent and twenty-two cases which he attributed to the inhalation of pollens; Flood and Perry^{11,12} in two separate articles reviewed thirty and thirteen cases, respectively, due to food allergy; and Livingood and Pillsbury¹⁷ reported twenty-one cases of hand involvement in twenty-six cases in whom food allergy was the only, or a significant contributory, factor. Barber,⁴ and Andrews and Machacek,² respectively, reported groups of cases of pustular bacterids; Benedek⁵ described a number of cases caused by infection with endoparasitic bacilli; and Blaisdell and Swartz⁶ reported 1.2 per cent of cases seen in private practice based on a mechanism depending upon the action of an endogenous toxin on the skin previously prepared by occupational exposure. Also eruptions resulting from pyogen sensitization have been described under various titles in separate articles by Burky and Hopkins,¹⁴ Lane and Rockwood,¹⁶ and Stokes and co-workers.²⁸ In addition, Winston³² presented his classification of the etiological agents of hand eruptions; Winston and Sutton³¹ studied 388 consecutive hand cases in the latter's private office and found that thirty presented characteristics that seemed to constitute a clinically recognizable dermatitis due to ingested food allergy; and Waldbott³⁰ gave his classification of patterns on the hands in a review of eighty-five cases. Recently, Samitz²² in a schematic presentation classified this group of eruptions according to chronicity, common or infrequent types, mechanism of causation and clinical attributes. In reviewing the first group of papers, one is impressed by the large number of cases reported for a single etiologic agent without any relation to the incidence of other etiologic types of hand eruptions. Although Winston,³² Sutton³¹ and Waldbott³⁰ offer some statistics, all the etiologic types are not considered in their articles.

This study was undertaken to complement the Samitz²² report, and it is hoped that the error one may make in assuming the frequency of any single type of hand eruption, exclusive of other etiological types, will be avoided. This study was restricted to office patients seen over a three-year period. Not included in this study were the groups of hand eruptions reported by Samitz and his co-workers,¹⁹⁻²⁷ in their surveys of the skin hazards of the commodity goods industries of the Philadelphia Industrial Centers.

From 1947-1949, a group of 403 cases diagnosed under the legend of

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

vesicular and pustular eruptions of the hands were reviewed. In this study, the following analysis was made (Table I):

TABLE I. ANALYSIS OF TOTAL CASES

Primary Diagnosis	No. of Cases	Percentage	No. of Cases with Associated Diagnoses
1. Primary irritants	210	52.1	81
2. Trichophytids	81	20.1	20
3. Epidermal sensitization	46	11.4	6
4. Nummular eczema	14	3.5	0
5. Primary fungus	13	3.2	2
6. (a.) Food allergy	13	3.2	7
(b.) Drug sensitization	3	0.7	0
7. Pyogen sensitization	6	1.5	4
8. Pustular psoriasis	5	1.2	0
9. Undiagnosed	5	1.2	..
10. Anhidrotic syndrome (miliaria; sweat retention syndrome)	4	1.0	1
11. Psychosomatic	2	0.5	0
12. Dermatitis repens	1	0.2	0
Total	403	100%	121

PRIMARY IRRITANTS

Over 50 per cent (210) of the cases reviewed fall into the classification of primary irritants. Jordan and his associates¹³ reported 239 cases in private practice in whom soaps appeared to be the exciting cause. In their study 61 per cent were housewives or domestics, while the remaining 39 per cent included such occupations as dishwashers, cooks, hairdressers, bartenders, surgeons, nurses, orderlies, and the like. Sulzberger and Baer²⁹ stressed that housewives are exposed to polishes, soaps, and other cleansers, all of which are definite irritants on pathologic skin. Patch tests with these agents and the localization of the eruption on the hands are of no help in the diagnosis. As a matter of fact, Sulzberger emphasized that "just as in allergic contact-type eczema of the hands, eczemas due to or maintained by primary irritants are prone to affect the interdigital webs, the sides of the fingers, and the dorsa of the hands, rather than the palms."

In this study, women were involved over men in the ratio of two to one. The most common age group was the twenty to fifty year group. Bilateral involvement was seen in about 80 per cent of the cases, and also in approximately 80 per cent previous local therapy had been received, either medical or self-treatment. The housewife and those with vocations and avocations necessitating exposure to soap and water, cleansing agents, and the like, were subject to this type of dermatitis of the hands. Housewives made up 60 per cent of this group. The duration of symptoms, prior to the initial visit to this office, ranged from one week to thirty years, with about 50 per cent being seen in the first five months of their disability. No definite line of demarcation between the acute and the chronic stage is made, if the time element alone is used as a criterion; that is, many cases of acute contact to primary irritants of one to two weeks may have all the features of a chronic fissured eczema and, in contrast, cases of many years' duration

may show features and attributes of an acute eczematous picture. Our findings in this series of cases substantiated those of Jordan and his co-workers in that these eruptions improved or flared depending on the degree and/or the frequency of exposure to these irritants. Especially involved was the hand that the patient more frequently used.

Following the schematic outline of therapy reviewed by Samitz,²² it was found that 92 per cent of these cases were discharged as sufficiently improved, or cured, within a period of two months. Emphasis was placed on complete protection of the hands with cotton and rubber gloves, and local therapy was dependent on the phase of the eruption. An interesting finding in a small number of cases of housewife's eczema was the reflare of the dermatitis despite the elimination of soap. These patients, however, continued to immerse their hands in water, i.e., Philadelphia water. However, if these patients moved temporarily to the seashore (during vacations) or used water from an adjoining county, improvement followed. One may postulate a synergistic action of soap and Philadelphia water (hard and highly chlorinated).

Eighty-one cases were associated with other etiological factors which also had to be treated. This implied that in over one third of the cases, to have treated the primary irritant condition only would have negated any satisfactory results in treatment. In all these cases the essential diagnosis was that of primary irritant, and the associated diagnoses were contributory causal factors. Epidermal sensitization (often alone, and occasionally associated with other etiological factors) made up over one third of these cases. Trichophytid, primary fungus (*Trichophyton purpureum*, *Candida albicans*), pyogen sensitization, and the anhidrotic syndrome were other contributory causal agents. Also, primary irritation was seen as a secondary factor in cases of food allergy and pyogen sensitization.

TRICHOPHYTIDS

Lane and his associates¹⁶ felt that "only a few of the eruptions on the hands are direct fungous infections of the hands or 'id' reactions to fungous infections of the feet." Wise and Wolf³³ stressed that since a large proportion of adults have, or have had, fungous infections of the feet, positive reactions to intradermal tests and patch tests with trichophytin are of little significance. "Id" reactions of the hands must be ascertained by showing the positive causative organism, microscopically or by culture from the primary focus. Andrews and Barnes,¹ reporting 200 cases involving the hands, listed forty-eight cases, or 24 per cent, due to fungus "ids." The feet in these cases were positive for fungi. Epstein¹⁰ doubted "if the diagnosis of dermatophytid is tenable in the absence of an active mycotic infection elsewhere on the cutaneous surface or of one affecting its appendages." Ayres and Anderson³ pointed out that "without laboratory confirmation, a diagnosis of fungous infections of the hands had 85 per cent chance of being wrong." Of 614 cases studied over a sixteen-

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

year period with direct microscopic examination, or by culture, in eruption of the hands, fungi of the *Trichophyton* group was recorded as 11.7 per cent. Cornbleet,⁹ classifying this group as eczematoid ringworm of the hands, listed this group as one of the four commonest hand dermatoses. He reported no statistics.

Eighty-one cases (about 20 per cent) of trichophytid of the hands were included in this study (Table I). The incidence was twice as frequent in men. Age differentiation and occupation were not informative. Seventy per cent of the patients in this group were seen within the first two months of their disability. The remaining number in this group, especially those with their symptoms present for a year or more, were those with recurrent episodes. Seventy-five per cent of the patients had had previous local therapy, and 12 per cent had had previous X-ray therapy. In the majority of cases (75 per cent), successful therapy was completed in a period of one month. In only eleven cases in this group were recurrences and seasonal factors a feature in the history. All diagnoses were substantiated by the following criteria:

1. Positive microscopic examination or culture from lesions on the feet.
2. History of an explosive picture on the hands following a flare at the primary source.
3. Improvement and cure of the hand eruption following the remission of the foot eruption.
4. Positive trichophytin test.

Epidermal sensitization to local treatment was a major cause in half the cases which had associated etiological factors. Also such factors as pyogen sensitization and anhidrotic syndrome prolonged the clinical course.

A secondary diagnosis of trichophytid was made in cases of primary irritancy, food allergy, and pyogen sensitization.

Treatment consisted of palliative measures for the hands with a specific fungicidal approach to the primary focus on the feet.

EPIDERMAL SENSITIZATION

Forty-six cases (about 11 per cent) of the total number of cases studied were primarily of this type. The causal factor in one third of the cases of epidermal sensitization was a topical medicament. Sulzberger²⁹ maintained "that topical therapeutic agents include some of the most common, and most commonly overlooked eczematogenic allergens which produce or maintain eczemas of the hands."

Of this group, the sexes were equally involved. The major age group was twenty to forty years. Symptoms varied from one week to twelve years; however, about three quarters of the cases in this group were seen within the first two months of their dermatitis. In many cases it had been

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

impossible to determine the initial dermatological complaint for which treatment had been given that had produced the sensitization. Rhus dermatitis and sensitization to cosmetics (a common occupational exposure in beauticians) followed as frequent offenders. Only six cases with the primary diagnosis of epidermal sensitization had associated diagnoses. Three cases were associated with anhidrotic syndrome of the hands; two, with pyogen sensitization; one, with primary fungus (*erosio interdigitalis blastomycetica*). Epidermal sensitization was noted as a secondary diagnosis in cases of primary irritancy, trichophytid, and food allergy.

Treatment was completed in most cases (over 90 per cent) within one month. Treatment consisted of the elimination or avoidance of all previous topical medicaments. Self-evident contactants, or those elicited by patch tests, were also avoided. Local therapy consisted essentially of simple compresses and bland ointments.

NUMMULAR ECZEMA

Nummular eczema, first described by Devergie (Brocq's "neurotic eczema," Pollitzer's "recurrent eczematoid affection of the hands," and Kriebach's "exudative neurodermatitis") presented itself in fourteen cases. Gross,¹³ in his comprehensive study of nummular eczema and the use of vitamin A therapy (eighteen satisfactory results in twenty-four patients studied), described the variability of the associated pruritus, the appearance or recurrence of nummular eczema in the cold season, with clearing in the summer, and stressed that asteatosis was a predisposing factor in nummular eczema. Sulzberger²⁹ listed the factors aggravating nummular eczema and included cold, drugs, primary irritants, friction, wool, oils, greases, and especially soap and water. He further stated that "in our clinical material, nummular eczema is among the most common eruptions of the hands." Cornbleet⁹ referred to nummular eczema as one of the four commonest dermatoses.

There were fourteen cases (3.5 per cent) of nummular eczema included in this study. No cases were seen in patients under twenty years of age. All cases of nummular eczema, but one, had been present for at least one year when initially seen. Half the cases had seasonal occurrences (winter). The length of treatment varied with the frequency of the recurrences. This was compatible with the known clinical picture of recurrences, chronicity, and stubbornness, characteristic of nummular eczema.

Treatment consisted of a prophylactic regime (glove technique); a viform paste locally; vitamin A orally; and crude liver parenterally. Occasionally, pruritus was controlled by an ethyl chloride spray, and resistant cases were treated with aureomycin (viral sensitization?).

PRIMARY FUNGUS

Thirteen cases (about 3 per cent) were classified as cases of primary fungus of the hands. Sulzberger²⁹ noted that primary fungus of the hands

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

is uncommon and that no particular site on the hands was characteristic or diagnostic. Andrews' study¹ revealed that direct fungus of the hands was seen in 2 per cent and direct fungus of the hands and feet in 1.5 per cent, or a total of 3.5 per cent. Carpenter⁷ referred to Light's study of a series of 600 patients at the New York Skin and Cancer Unit where primary fungus was found in 2 per cent of the patients.

Sex, age, and occupational factors were not informative in this group of cases. In most instances, the duration of symptoms was one year or more before medical treatment was sought. All the cases had had previous local therapy, and half the cases had had x-ray therapy. Nine cases showed unilateral involvement, while four cases were bilateral. The feet were involved in seven cases. All the diagnoses were substantiated by positive scrapings and positive cultures. *Trichophyton purpureum* was the causative agent in eleven cases, and *Candida albicans* was demonstrated in two cases. The associated diagnosis of onychomycosis occurred in two cases of the *Trichophyton* group. Primary fungus was noted as a secondary diagnosis in cases of primary irritancy and epidermal sensitization.

Therapy was directed towards the avoidance of alkaline soaps and the application of fungicidal agents.

FOOD ALLERGY

Rowe¹⁸ reported eighty cases in a series of 182 patients with dermatitis of the hands seen in the private practice of allergy in whom the allergy and the dermatitis were attributed to foods. He also cited eczematous dermatitis of the hands due to allergy to inhaled pollens as a major or secondary cause in twenty-two of these patients. He referred to Lane and his associates,¹⁶ with whom he agreed that "dermatomycoses, dermatophytid, contact dermatitis, or soap dermatitis are responsible in only a few of the cases of the 'eczematoid' dermatitis of the hands." Rowe is convinced that atopic allergy to food, especially, and much less to pollens, is responsible for many of the large number of eruptions which Lane and his associates called "the cause of which was not known." Flood and Perry's¹¹ study of recalcitrant vesicular eruptions of the hands due to food allergy consisted of cases drawn from a large series of cases in which the dermatitis persisted after other causal factors were removed and in which prolonged local therapy had been ineffective. They presented thirty cases, and all their subjects, with two exceptions, were studied in the hospital. In the series studied by Livingood and Pillsbury,¹⁷ the hands were involved in twenty-one of the twenty-six patients and the hands were involved alone in only ten of the twenty-six patients. Sulzberger²⁹ emphasized that "unless the patients can be hospitalized and kept under strictest dietary surveillance, reliable and accurate evaluation of the effects of dietary changes in eczema of the hands is an extremely difficult task."

The thirteen cases of food allergy studied in this series were all treated on an office regime. The following routine was used: (1) a basic diet of

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

seventeen foods of low allergenic index, and (2) a food diary maintained by the patient, noting any subjective or objective changes of the hands. No attempt was made to evaluate these cases by means of the pulse recording following the consumption of food, as described by Coca.⁸ Our findings parallel those of other observers in that the condition is more common in women (in this series ten to three); the symptoms were chronic, and half the cases were of four years' duration or longer. The distribution and the clinical attributes of the lesions were similar to that described by other observers. In seven of the thirteen cases there were associated diagnoses, and therapy was also directed to these etiological factors. Only two cases showed a seasonal flare. No attempt was made to determine the association with pollens in any of these cases.

Egg and milk were the major offenders, seen alone or in combination with other allergens, in ten of the thirteen cases. Wheat, chocolate, and orange juice were also noted as factors. In one case, immediate relief was noted and progressive improvement followed use of the basic diet. However, after the eruption had cleared on the elimination diet, the subsequent addition of the suspected offending foods did not produce a recurrence of the dermatitis. It appeared that a cycle was broken or that spontaneous desensitization followed. Most of the cases cleared within three months. The cases lasting longer were in those patients who willingly, or unknowingly, ingested the offending foods. Various attempts of desensitization were made and will be reviewed in a subsequent paper.

Three cases of drug sensitization were noted: two to penicillin and one to sodium amytal. After the diagnoses were made, treatment consisted of elimination of the drug and palliative local measures.

PYOGEN SENSITIZATION

Six cases of primary pyogen sensitization were studied. This small group was predominantly in men five to one, and all the cases occurred in the twenty-eight to thirty-eight-year age group. All had had previous treatment before their initial visit and all showed bilateral involvement. Associated diagnoses of primary irritancy and fungous sensitization were noted in four of the six cases. Pyogen sensitization was seen as a secondary diagnosis in cases of primary irritancy, trichophytids, food allergy, and epidermal sensitization. Pyogen sensitization has been an outstanding factor in perpetuating an eruption of the hands beyond its usual duration. It has appeared to be the trigger factor necessary to maintain an eruption into chronicity. All these cases were highly sensitive to staphylococcus toxoid. Bacteriostatic and bacteriocidal agents were used locally, and desensitization was carried out with staphylococcus ambotoxoid.

PUSTULAR PSORIASIS

Five cases (1 per cent were examples of the entity known as pustular psoriasis. Two of the five cases subsequently developed guttate lesions

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

of psoriasis. The duration of symptoms before seeking treatment ranged from two to five years. All had had local treatment and four of the five cases, x-ray treatment. These cases were characterized by recurring pustules which dried up to form the characteristic brownish scabs. Therapy was unsatisfactory. These cases are not to be confused with the pustular bacterids of Andrews, of which there were none in this series.

ANHIDROTIC SYNDROME (MILIARIA; SWEAT RETENTION SYNDROME)

Anhidrotic syndrome localized to the hands was seen in four cases (about 1 per cent). Three of the four cases were in the thirty-one to forty-year group. One case was associated with symmetric erythema of the hands and feet. This syndrome was seen as a reaction to hot weather, friction, excessive sweating, and as an end result of chemical irritants and sensitizers. These factors were productive of a faulty keratinization and occlusion of the sweat pores, with sweat retained in the ducts. It had sudden onsets and spontaneous remissions; burning, pricking, and itching was a feature; and the pinhead-sized vesicles were more marked along the lateral margins of the fingers and the hypothenar areas.

Anhidrotic syndrome was noted as a secondary diagnosis in cases of primary irritancy, trichophytid, epidermal sensitization, and food allergy.

Treatment consisted of the application of cool compresses and keratolytic tinctures, and placing of the hands in a special air-conditioning unit for the hands.

MISCELLANEOUS

One case of dermatitis repens was recorded in this series. This case had persisted for eight years, and previous therapy was intensive and ineffectual.

Two cases of psychosomatic etiology were observed. The symptoms in both were present on different occasions for three years. The eruption in one case appeared with any form of stress; the second was due to maternal stress.

In this total of 403 cases studied, five cases were classified as undiagnosed and were treatment failures.

COMMENT

Samitz presented a schematic outline of eruptions of the hands in a previous publication,²² for it was felt that a practical concept of hand eruptions was necessary. To cement this concept, a review of 403 consecutive cases was made of all such hand eruptions seen in the office (M.H.S.) during a three-year period, 1947-1949. No attempt was made to select cases. The primary etiologic diagnosis was the major one presenting itself for treatment. To have treated these cases without regard for the associated etiologic diagnoses would in most instances have meant treatment-resistant cases. At times the differentiation between acute and chronic eruptions depending on a time element was uncertain, for instances

ECZEMATOUS HAND ERUPTIONS—SAMITZ AND ALBOM

of chronic fissured eczema developed in short periods of time, whereas many eruptions of long duration still maintained the attributes of acute eczemas. In most cases a careful consideration of a hand eruption involved a careful history, examination, and an adequate laboratory study. It might be emphasized that "snap" diagnoses reached by a "quick look" at a hand eruption would in most cases result in an erroneous diagnosis. In many of the cases studied, manifold causal factors presented themselves for consideration on the first visit, and after careful consideration of these, several etiologic mechanisms were prominent. Response to a fixed or closed dressing technique helped in the elimination of primary irritants or epidermal sensitizers as possible causal agents. Further observation and testing was required to define the eruption to one of the other etiologic categories. The realm of hand eruptions presents the same considerations, pitfalls, and diagnostic acumen for the dermatologist that is seen in the differential problems confronting the internist.

SUMMARY

Seen over a three-year period, 403 consecutive private cases of eczematous and pustular eruptions of the hands were studied. The etiologic mechanism was established in 398 cases. Of this series, 121 cases showed multiple causal factors. In five cases, a definitive etiologic diagnosis was not reached. The major groups were primary irritants, trichophytids, and epidermal sensitizers. In decreasing frequency cases of nummular eczema, primary fungus, and food allergy were seen. Cases of pyogen sensitization, pustular psoriasis, anhidrotic syndrome, drug sensitization, psychosomatic factors, and dermatitis repens were also observed. Emphasis is directed at the multiple etiologic factors that can be present and the understanding of the synergistic interplay of contact, fungus, pyogen, virus, and food allergy, and those of emotion, sweat, soap and water. A proper etiologic diagnosis and the elimination of each potential contributory factor are essential for the specific and adequate treatment of eczematous eruptions of the hands.

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A NEW METHOD AND MEDIUM FOR ADMINISTERING AND CONTROLLING THE ACTION OF THERAPEUTIC AGENTS, WITH PARTICULAR REFERENCE TO EPINEPHRINE

I. Experimental Studies

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IN order to investigate the possibility that the assimilation and absorption, as well as the therapeutic action, of various medications might be altered and controlled by combining them with solutions of algin, whose properties are unusual, a series of experiments are being carried out, some of which are reported here. As this is a new medical concept, a review of some of the unique properties and the commercial uses of algin follows.

Algin* is the common name for alginic acid and its derivatives: namely, the sodium, potassium, ammonium, and calcium salts, as well as certain esters such as the propylene glycol ester. The latter product, known as propylene glycol alginate, has been extensively used in these experiments. (Propylene glycol, as well as other propylene glycol esters, has been shown in previous studies to have no significant toxic effects¹). Alginic acid is the hydrophilic colloidal polymer of anhydro-B-D-mannuronic acid and is extracted from various species of brown algae. It is primarily derived from giant kelp, *Macrocystis pyrifera*.

It is possible to greatly increase the viscosity of aqueous solutions by the addition of small amounts of algin. Thus algin gives viscous aqueous solutions at relatively low concentrations (Fig. 1). Because of these and other unique properties, algin products are used as thickening, suspending, stabilizing, emulsifying, gel producing, film forming, and adhesive agents in numerous food and industrial products. In general, they are found in such foods as ice creams, sherbets, ices, chocolate milk, cheeses, puddings, bakery goods, confections, jellies and syrups, breads, et cetera. They are used in industrial products such as paper coatings and sizings, adhesives, textile printing, water emulsion paints, boiler compounds, detergents, polishes, et cetera. They can also be used in creaming and thickening natural and synthetic rubber lattices and rubber compositions and in water paints. Shampoos, shaving creams, and toothpastes often contain algin. Dental impression compositions frequently contain potassium alginate. The propylene glycol alginate is used mainly in flavor emulsions, salad dressings, meat sauces, meringues, syrups, and toppings.

Algin solutions do not coagulate on heating nor gel on cooling but maintain their smooth flow characteristics over wide temperature ranges. They readily dissolve in hot or cold water, allowing for ease of parenteral administration with syringe and needle. They are free of nitrogen and have

*Acknowledgment of indebtedness and thanks are due the staff and management of the Kelco Company of San Diego, manufacturers of Algin, without whose co-operation and helpfulness this work would not have been possible.

CONTROL OF THERAPEUTIC AGENTS—OUER

a low allergenicity.² They are clear and colorless, and have a moderately high molecular weight.

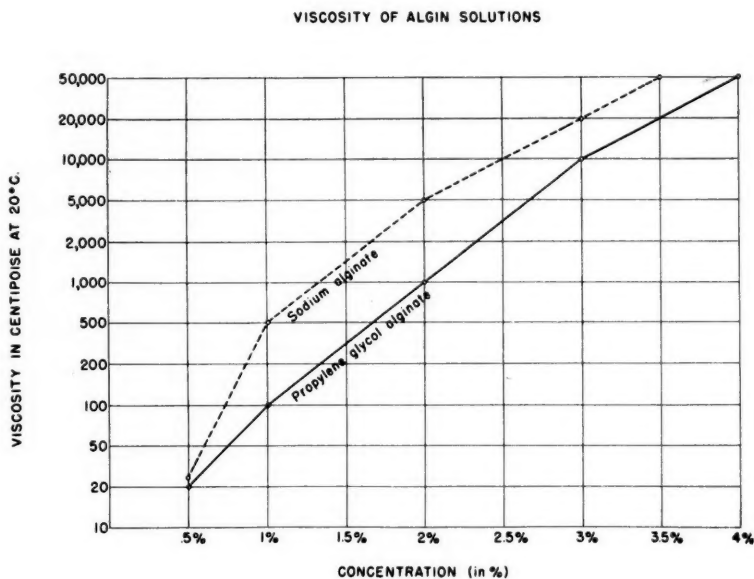


Fig. 1

ALGIN SOLUTIONS FOR PARENTERAL USE

It was possible to prepare water solutions of algin with varying viscosities which could be made physiological by the addition of appropriate amounts of sodium chloride. Sterility was maintained by the addition of chlorbutanol and/or phenol, and it was felt that these solutions might be satisfactory for controlling the assimilation and action of therapeutic agents. (Some of the solutions used were autoclaved for sterility and others were chemically sterilized. Bacteriological studies revealed that either method was satisfactory for preparing and maintaining sterile solutions.) The original toxicity studies were carried out mainly with the propylene glycol alginate, although the sodium alginate was also used occasionally.

TOXICITY STUDIES

For injection into animals aqueous solutions containing algin which varied in concentration from 0.5 to 3 per cent were sterilely prepared. Nine-tenths per cent sodium chloride and 0.1 per cent phenol was added.

At levels of 1 to 2.5 per cent the solutions were easily injectable. Rabbits were injected subcutaneously, intramuscularly, and intraperitoneally, using $\frac{1}{2}$ cc, 1 cc, and 2 cc amounts. Propylene glycol alginate was also injected

CONTROL OF THERAPEUTIC AGENTS—OUER

up to 2 cc amounts intravenously. No toxic responses were noted in the animals, and the areas of subcutaneous and intramuscular injections showed no hyperemia or induration on gross examination. Microscopic tissue sections of the injected areas revealed nothing unusual. No abnormal systemic effects were noted in any of the animals injected intravenously. It was noted that the more viscid solutions were more slowly absorbed from the subcutaneous areas.

At this writing, animals have received intraperitoneal total doses of 2 per cent propylene glycol alginate up to 375 milligrams per kilogram of body weight without lethal effect or disturbance of normal activities. Additional toxicity experiments are being carried out and will be reported later.

COMBINATIONS OF ALGIN AND THERAPEUTIC AGENTS

It was found that it is possible to prepare a variety of medications in combination with sterile, saline, algin solutions. Some of these drugs are listed below:

- | | |
|---|----------------------------|
| 1. Medications for Allergic Diseases: | 6. Anticoagulants: |
| Epinephrine Histamine | Heparin |
| Ephedrine Allergenic extracts | Dicumarol |
| Antihistamines (injectable) | 7. Vitamines: |
| Aminophylline (injectable and as suppository) | Thiamine chloride |
| 2. Antibiotics: | Ascorbic acid, et cetera |
| Penicillin | 8. Analgesics: |
| Streptomycin, et cetera | Morphine |
| 3. Sulfa Drugs: | Codein |
| Sodium sulfathiazole, et cetera | Papaverine |
| 4. Hormones: | Salicylates |
| Insulin | 9. Hypnotics: |
| Estrogens and androgens | Bromides |
| Pituitary extracts | Barbitals |
| Adrenal cortical extracts | Chloral hydrate, et cetera |
| 5. Cardiac Drugs: | 10. Local Anesthetics: |
| Digitalis | Cocaine |
| Xanthines | Novocaine, et cetera |
| Nitrites | 11. Miscellaneous: |
| Caffein, et cetera | Atropine |
| | Ergotamine |
| | Liver extracts, et cetera |

This partial list will indicate the wide range of applicability of these solutions. In addition to preparing medications for injectable use it was also possible to prepare topical medicaments, suppositories, oral medications, et cetera. At the present time it is felt that it is possible to combine mixtures of most water-soluble medications with an algin solution.

It has also been possible to prepare mixtures of oily suspensions with aqueous solutions and hold them in an emulsified state or colloidal suspension. This, however, opens another field for further investigation. Of pri-

CONTROL OF THERAPEUTIC AGENTS—OUER

mary interest for the purposes of this paper are the results of experiments with algin solutions containing epinephrine.

METHOD OF STUDY

Algin solutions of varying percentages in combination with different strengths of epinephrine were prepared. Examples of such solutions herewith follow:

Solution A.—Epinephrine hydrochloride (1:1000), 1.75 per cent propylene glycol alginate, plus 0.45 per cent phenol, plus 0.05 per cent chlorbutanol, plus 0.01 per cent sodium bisulphite, in a water solution.

Solution B.—Epinephrine hydrochloride (1:200), plus 0.875 per cent sodium alginate, plus 0.45 per cent phenol, plus 0.05 per cent chlorbutanol, plus 0.01 per cent sodium bisulphite, plus 0.9 per cent sodium chloride, in a water solution.

Solution J.—Epinephrine hydrochloride (1:1000), plus 1.25 per cent propylene glycol alginate, plus 0.9 per cent sodium chloride, plus 0.5 per cent phenol, in a water solution.

Solution K.—Epinephrine hydrochloride (1:1000), plus 1.5 per cent propylene glycol alginate, plus 0.9 per cent sodium chloride, plus 0.5 per cent phenol, in a water solution.

Solution F2.—Epinephrine hydrochloride (1:500), plus 2.25 per cent propylene glycol alginate, 0.45 per cent phenol, 0.05 per cent chlorbutanol, 0.01 per cent sodium bisulphite, 0.89 per cent sodium chloride, in a water solution.

It is to be noted that the solutions of epinephrine hydrochloride varied from 1:200 to 1:1000 in strength and that the concentrations of algin varied from 0.8 per cent to 2.25 per cent.

Hereafter, to avoid verbosity, the term "algin-ephrin" will be used to designate aqueous solutions containing algin in various concentrations with epinephrine of varying strength, made physiological by the addition of sodium chloride, sterilely prepared and containing chlorbutanol and/or phenol, as well as sodium bisulphite for color stabilization.

These substances were injected in equivalent amounts subcutaneously into fasting rabbits, and the level of blood sugar at fifteen-minute intervals thereafter was used as an index of the physiologic response. Also noted was the respiratory rate, pulse rate, and reaction of nervousness in the animal. These reactions were found to coincide with the blood sugar levels, and it was therefore felt that the level of blood sugar was a good index of epinephrine response.

As a control, animals were injected with equivalent amounts of plain epinephrine hydrochloride, 1:1000. Animals not receiving any medication were also subjected to injection and removal of blood samples, which were tested to note the effect on the blood sugar levels of handling and inserting the needle.

Also as a comparative study, algin solutions containing insulin were

CONTROL OF THERAPEUTIC AGENTS—OUER

injected into rabbits and subsequent blood sugar levels determined. (As a control, animals were injected with equivalent amounts of regular insulin). Although this is a portion of another research problem, the results are included here because they illustrate a contrasting effect upon the blood sugar.

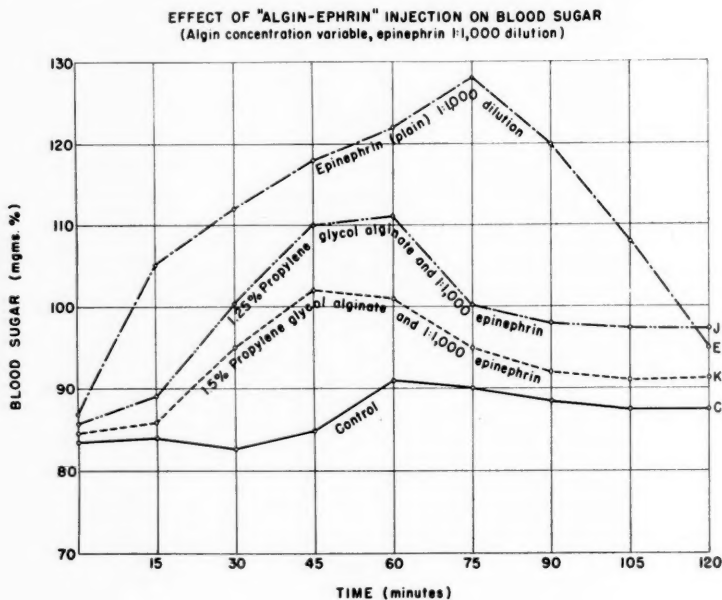


Fig. 2

RESULTS OF STUDY

Figure 2 illustrates blood sugar curves where the levels of blood sugar in milligrams per cent are charted against time. Solutions of plain epinephrine and algin solutions of varying concentrations containing epinephrine in strengths of 1:1000 are charted. Plain epinephrine (1:1000) yielded the most rapid rise and fall and the highest level of blood sugar. Epinephrine (1:1000) in solution with algin yields a less rapid rise in blood sugar with a lower maximum rise and a slower fall of blood sugar. The greater the algin concentration the slower the rise and fall of the blood sugar and the lower the maximum rise in level.

Figure 3 indicates a comparison of the action of "algin-ephrin" (with an epinephrine strength of 1:500 and an algin concentration of 2.25 per cent) with a conventional suspension of epinephrine in oil (1:500).

A comparison is also made with an 0.8 per cent sodium alginate solution containing epinephrine in a 1:200 dilution. It will be noted that this solution is not much more active than the epinephrine-in-oil (1:500), although

CONTROL OF THERAPEUTIC AGENTS—OUER

it is more than twice as strong, and it is more slowly absorbed than plain epinephrine (1:1000); although it is five times as strong. Its action also is slightly prolonged over that of epinephrine-in-oil. The 1:500 epinephrine solution with 2.25 per cent algin concentration is more slowly absorbed than any of the other preparations, including the epinephrine-in-oil. This

COMPARISON OF "ALGIN-EPHRIN" SOLUTIONS AND SUSPENSION OF EPINEPHRIN IN OIL

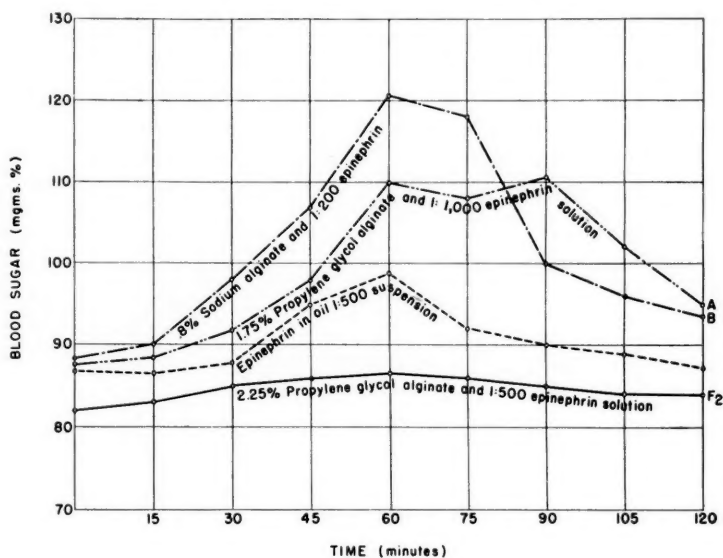


Fig. 3

is probably due to the high concentration of algin present. If such high concentrations of algin are to be used, it will probably be necessary to use higher concentrations of active principle (medication) to obtain greater effects. (However, this indicates that if very slow absorption is desired, it can be accomplished). The algin solution (A) in this figure containing 1.75 per cent algin and 1:1000 epinephrine is more active than the epinephrine-in-oil (1:500) and attains a later peak of activity and a slower fall of sugar level, indicating a more prolonged action.

Figure 4 illustrates the effect on the blood sugar of the injection of "algin-insulin" solutions. It will be noted that the insulin mixtures containing algin protected the animals from a rapid fall of blood sugar and death from insulin shock and that the slow lowering of the blood sugar levels was a result of the presence of algin in the solution.

CONCLUSIONS

The results of these experiments indicate that the physiological activity of epinephrine (as well as insulin) is dependent upon the concentration of

CONTROL OF THERAPEUTIC AGENTS—OVER

algin contained in the solutions; the greater the concentration of algin the slower the absorption, assimilation, and resultant physiological responses. The effect on pulse rate, respiratory rate, nervousness, et cetera, paralleled the effect on blood sugar.

It is possible to administer larger doses of epinephrine in the form of

EFFECT OF "ALG-INSULIN" SOLUTIONS ON BLOOD SUGAR

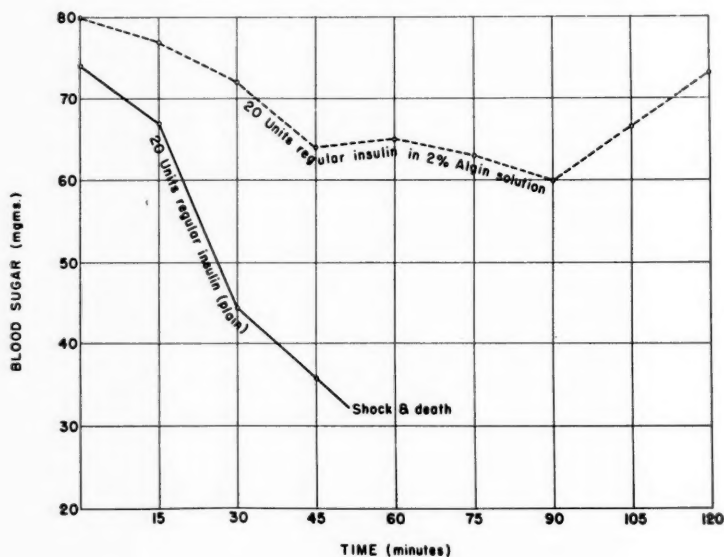


Fig. 4

"algin-ephrin" solutions than are conventionally used. A wide range of physiological response is possible by varying the concentration of algin in the solutions.

DISCUSSION

The preparations described are new and unique in their properties and action. They are water soluble and can be made physiological by the addition of sodium chloride. They are easily absorbed, nontoxic, and also free of nitrogen, thus minimizing allergic reactivity. Relatively small concentrations of the algin are necessary to obtain the desired effect. They are nonirritating, painless to administer, relatively inexpensive to prepare, and easily injected without preparatory manipulations, such as shaking or warming. They are pure, colorless solutions, easily sterilized, free of undesirable foreign matter, and stable within a wide temperature range. The viscosity can be controlled as desired by varying the concentration of the algin, and there is a wide range of physiological effects which can be at-

CONTROL OF THERAPEUTIC AGENTS—OUER

tained. The activity of any one mixture is relatively constant, varying only slightly with the individual. The active principles (medications) are present in solution and apparently remain in the soluble form.

The disadvantages of the conventional so-called "slow acting" preparations, such as insolubility in water or saline solution, irritation and discomfort at site of injection, toxicity, allergic reactions, and the presence of foreign matter, are not present with "algin-ephrin." Frequently in the conventional preparations the epinephrine is suspended in a vehicle such as oil or gel. This often leads to variable physiological response unless precautions are taken in handling, preparing, and administering the preparation. The vehicle itself must be eliminated as foreign matter. The conventional preparations require warming, shaking, and other processing before administration. These disadvantages are eliminated in the "algin-ephrin" preparations.

SUMMARY

A new medium for administration of therapeutic agents has been described, comprising a water or saline solution containing algin in varying concentrations and combined with medications of various strengths.

It is possible to control the viscosity, as well as the absorption, assimilation, and physiological action of the medications by varying the concentration of algin in the solution. Only small amounts of algin are necessary to obtain a wide range of physiologic activity.

These solutions are adaptable to a wide range of drugs, since most soluble medications can be combined in these mixtures. It is possible to vary the strength of the drug as well as to vary the concentration of algin in the solution. The advantages of having two variables for the control of activity are obvious.

It has been shown that doses of drugs larger than conventionally used can be given and that the action can be prolonged or modified. The greater the algin concentration, the more viscous the solution, and the slower the absorption and physiologic response to the medication.

"Algin-ephrin," a water or saline solution containing epinephrine in various strengths and algin in various concentrations, has been tested for physiologic activity and has been demonstrated to have a wide range of physiologic response which can be controlled. These solutions allow for greater dosage of epinephrine than heretofore used and also for a wider range of therapeutic effect as well as prolongation of therapeutic action. These solutions have been prepared as an aid in the treatment of allergic disorders and to date clinical experiments have been most encouraging.

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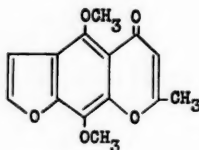
OBSERVATIONS ON THE ACTION OF KHELLIN IN ATTACKS OF BRONCHIAL ASTHMA

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KHELLIN is obtained from the plant *Ammi Visnaga* Lam., known in Arabic as "Khella" and in English as "Bishop's Weed." It is a member of the carrot family, a large group of plants that includes parsley, parsnip, celery, and several aromatic herbs such as anise, caraway, and dill.¹¹ In Egypt and the Mediterranean littoral, a decoction of the dried seeds has been used from ancient times as a diuretic and as an antispasmodic in the relief of ureteral stones.

Khellin has been synthesized by several groups of investigators.^{2,3,6} The empiric formula is $C_{14}H_{12}O_4$, the chemical name, 2-methyl-5, 8-dimethoxy-furanochromone, and the structural formula:



Reference to the drug has appeared in medical literature since 1879,⁷ but little interest was evoked until after pharmacologic studies had been published by Samaan in 1930-1932.^{8,9,10} This investigator reported that khellin (or visammin, as he called it), "relaxes all smooth muscle investigated by direct action on the muscle fibres—toad's blood vessels, mesenteric vein of sheep, rabbit's intestine, guinea pig and rabbit's uteri, bronchial muscle of the pig and of the dog, and the ureters of the pig, bull, cow and man."¹⁰

One of the first reports of the use of khellin in bronchial asthma was that of Anrep and associates.¹ These workers found that a single intramuscular injection of 200 to 300 mg khellin gave complete and prolonged relief in forty-one of forty-five severe cases; three cases required a second injection given one hour later; one case, complicated by bilateral pulmonary tuberculosis, double phrenic evulsion and thoracoplasty, failed to obtain relief. The authors stated that complete relief, which usually lasted about twenty-four hours, was given five to fifteen minutes after injection. Daily administration, by injection or by mouth, conspicuously reduced the number and severity of attacks. In obstinate cases of severe status asthmaticus, a

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KHELLIN IN BRONCHIAL ASTHMA—DERBES ET AL

TABLE I. CLINIC PATIENTS WITH BRONCHIAL ASTHMA TREATED WITH 100 MG KHELLIN ADMINISTERED INTRAMUSCULARLY

Case	Age	Sex	Race	Duration of Asthma	Present Attack	Blood Pressure		Time Required for Optimal Relief	Side Effects	Results
						Adm.	Disch.			
1	33	M	C	5 yrs.	3 days moderate	108/60	100/70	2 hours	Nausea	Excellent
2	22	M	C	12 yrs.	7 hours mod. severe	110/70	100/70			Slight or no benefit
3	32	M	C	5 yrs.	12 hours moderate	108/70	120/75		Injection site pain	Slight or no benefit
4	22	F	C	13 yrs.	24 hours very severe	110/80	122/70		Injection site pain—head-ache	No benefit
5	40	M	C	3 yrs.	3 days moderate	134/88	130/86	1 hour	Head-ache	Good
6	23	F	W	18 yrs.	4 days severe	120/76	124/80		Head-ache	No benefit
7	23	F	C	3 yrs.	18 hours severe	106/80	110/80	3 hours		Good
8	75	M	W	8 yrs.	1 hour moderate	170/100	166/100	2 ¼ hours		Excellent
9	37	F	C	2 yrs.	24 hours moderate	126/84	120/80	1 hour		Good
10	25	F	C	19 yrs.	15 hours moderate	126/86	120/90	1 hour		Excellent
11	38	M	W	14 yrs.	24 hours mod. severe	130/80	128/90			Slight improvement
12	24	F	W	8 yrs.	9 ½ hours moderate	120/84	130/90			No benefit
13	30	M	C	25 yrs.	2 ½ hours moderate	100/70	98/70	1 hour		Good
14	35	M	C	15 yrs.	2 days very severe	100/75	102/70			No benefit
15	41	M	C	1 yr.	7 ½ hours mod. severe	120/85	120/80			No benefit
16	25	F	C	1 yr.	3 days moderate	105/65	110/70	2 ½ hours		Good
17	37	M	C	15 yrs.	1 day mild	115/80	118/80	1 ½ hours		Excellent
18	18	M	C	12 yrs.	3 hours mild	90/65	95/65	½ hour		Excellent
19	53	M	C	50 yrs.	2 weeks moderate	112/78	116/82	¾ hour	Injection site pain	Good
20	36	F	C	4 yrs.	30 hours moderate	118/84	110/76	20 min.	Injection site pain	Good

second or third dose, at one to two hour intervals, was required to produce relief. Khellin relieved some cases which had been resistant to epinephrine and aminophylline. Although khellin action was not as prompt, it was more lasting than that of epinephrine or ephedrine, had no effect on blood pressure, and could be "safely administered even in hypertensive patients."¹

Two articles on the use of khellin in bronchial asthma have appeared in American publications. The first, by Major,⁵ reported twelve cases treated by the oral administration of 200 mg khellin twice daily or, in exceptional cases, three times daily. All of these patients were severely asthmatic. Only large doses of epinephrine or aminophylline—in some instances so large as to be potentially dangerous—had given relief during attacks, several obtaining only fleeting or no relief. None had been relieved by Benadryl or Pyribenzamine. All of these patients, with the exception of one who could not take the drug, obtained marked relief from khellin. In most instances the relief was rapid and was maintained for as long as the patient continued to take the drug.⁵

KHELLIN IN BRONCHIAL ASTHMA—DERBES ET AL

The other article reported work done in Egypt by Kenawy and his co-workers.⁴ Khellin was administered intramuscularly or orally to 138 patients with bronchial asthma. In most instances 200 mg was given intramuscularly, with definite relief in five to fifteen minutes. As a rule, orally administered khellin was used for maintenance after patients were dismissed from the hospital. The following results were obtained: complete relief, 102 patients (74 per cent); partial relief, 24 patients (17 per cent); no relief, 12 patients (9 per cent).⁴

METHODS AND MATERIAL USED IN THIS STUDY

Khellin* was administered, in 100 mg doses, to twenty patients by the intramuscular route and to twenty-five patients by the oral route. In the absence of improvement, this dose was repeated. All patients were kept under direct observation during the experimental period. The chest was auscultated repeatedly and, in the majority of instances, the blood pressure was determined a number of times. Table I shows the findings and results of therapy in twenty patients who received khellin intramuscularly.

OBSERVATIONS ON PATIENTS

The following case reports illustrate the different types of results obtained in the series of patients who were given khellin intramuscularly.

Case 10.—A woman, colored, aged twenty-five. Asthma for nineteen years; worse in winter and with colds. Is receiving treatment in an allergy clinic. Present attack began fifteen hours prior to admission. Two ephedrine capsules ($\frac{3}{8}$ gr) had been taken the night before.

Admission.—Mild to moderate attack; sonorous râles, expiratory wheezing; pulse 124; blood pressure 126/86.

1:10 P.M.—100 mg khellin, i.m.

1:35 P.M.—Subjectively much better—able to cough up some phlegm—râles and wheezing almost gone—pulse 116—blood pressure 130/84.

2:10 P.M.—Complete subjective relief—no objective findings—pulse 120—blood pressure 120/90—discharged.

Classification.—Excellent result.

Case 1.—A man, colored, aged thirty-three, unemployed. Asthma for five years; worse in winter. Has received allergy injections (type unknown). Present attack began three days ago; has received epinephrine, aminophylline, phenobarbital, atropine and infusion with aminophylline. Intravenous aminophylline last given at 7:30 A.M.

Admission.—Moderate attack; afebrile; bilateral sibilant and sonorous râles; marked kyphosis of lower thoracic and upper lumbar vertebrae; blood pressure 108/60.

11:15 A.M.—100 mg khellin, i.m.

11:45 A.M.—Slight subjective improvement—blood pressure 100/60—nausea.

*Khellin ("Eskel" used in this study is a mixture of active principles, chiefly khellin, extracted from *Ammi Visnaga* Lam., and was supplied by the Research Division of Smith, Kline and French Laboratories, Philadelphia.

KHELLIN IN BRONCHIAL ASTHMA—DERBES ET AL

12:15 P.M.—Subjective improvement—no objective improvement—blood pressure 105/60—"appears flushed."

12:40 P.M.—Subjective improvement—blood pressure 100/70—discharged. Seen at clinic next day. States attack subsided thirty minutes after discharge. No asthma since that time.

Classification.—Excellent result.

Case 9.—A woman, colored, aged thirty-seven. Bronchial asthma for two years; worse in winter. Has been treated in an allergy clinic, type of allergy undetermined. Present attack began twenty-four hours ago. Has taken two Amesecs, which gave temporary relief. No medication taken after attack recurred seven hours before admission.

Admission.—Moderate attack; sonorous and sibilant râles; pulse 88; blood pressure 126/84.

1:45 A.M.—100 mg khellin, i.m.

2:15 A.M.—Subjectively much improved—râles have decreased in intensity and concentration—blood pressure 120/80.

2:45 A.M.—Patient "feeling all right"—some auscultatory wheezing still present—blood pressure 120/80—discharged.

Classification.—Good result.

Case 11.—A man, white, aged thirty-eight. Present attack began twenty-four hours before admission. Had two 15-minim injections of adrenaline when attack began.

Admission.—Moderately severe attack; sibilant and sonorous râles; pulse 108; blood pressure 130/80.

1:30 P.M.—100 mg khellin, i.m.

1:55 P.M.—Breathing easier—subjectively slightly improved—râles still present—pulse 104—blood pressure 128/90—discharged himself.

3:50 P.M.—Returned with improvement. Refused further medication.

Classification.—Slight improvement.

Case 14.—A man, colored, aged thirty-five, hospital attendant. Asthma for fifteen years, mainly in winter and spring. Has received injections for house dust for the past fifteen months. Present attack began about two days ago; since onset, has received three Benadryl capsules, aminophylline intravenously three times, five aminophylline suppositories and 30 cc epinephrine. Aminophylline and epinephrine were last given at 7:20 A.M.

Admission.—Severe attack; sibilant and sonorous râles and rhonchi, bilaterally; afebrile; blood pressure 110/80.

9:20 A.M.—100 mg khellin, i.m.

9:45 A.M.—No relief—blood pressure 100/75.

10:00 A.M.—Subjective "lightening of attack"—patient breathing easier and not so apprehensive—no objective improvement—blood pressure 105/80.

10:20 A.M.—Worse after walking to treatment room—coughing—no subjective or objective improvement—patient states medicine has "opened his nose"—blood pressure 105/80.

11:00 A.M.—Subjectively "relieved a little"—additional khellin, 100 mg, i.m.

11:25 A.M.—Blood pressure 110/70.

11:45 A.M.—Subjectively improved—little objective change—blood pressure 108/75.

12:20 P.M.—Condition the same—blood pressure 110/70.

12:30 P.M.—Worse—blood pressure 108/70.

12:50 P.M.—Unimproved—blood pressure 110/70.

KHELLIN IN BRONCHIAL ASTHMA—DERBES ET AL

1:00 P.M.—Ephedrine, $\frac{3}{4}$ gr—no relief.

1:20 P.M.—Aminophylline, 0.25 gm i.v.—blood pressure 102/70.

1:30 P.M.—Much improved subjectively.

2:30 P.M.—Aminophylline, 0.25 gm i.v.—discharged.

Was seen at the clinic the next day. Reported sleeping all night. Subjectively over attack. Numerous sibilant and sonorous râles still present bilaterally.

Classification.—No benefit.

The twenty-five patients with bronchial asthma, who were treated by means of 100 mg doses of khellin given orally, were handled in the same manner as that used for patients receiving the drug intramuscularly. Table II summarizes the results obtained from khellin therapy in both groups of patients.

TABLE II. RESULTS OF KHELLIN THERAPY
IN 45 CLINIC PATIENTS

Route of Administration	Excellent		Good		Poor	
	No.	%	No.	%	No.	%
Intramuscular	5	25	7	35	8	40
Oral	5	20	9	36	11	44

DISCUSSION

Of the twenty patients to whom khellin was given intramuscularly, good or excellent results were experienced by twelve and slight or no benefit by eight. Similarly, of the twenty-five patients who were given khellin by mouth while under observation, good or excellent results were had by fourteen and slight or no benefit by eleven. The percentage of patients benefited is almost the same in both groups, i.e., 60 per cent.

Regardless of the route of administration, those cases in which khellin was most effective showed beneficial effects within twenty to thirty minutes, the attack terminating within sixty to ninety minutes (cf. Case 10). In more resistant cases, two to three hours elapsed before improvement was shown; in some cases the khellin dosage was repeated one or more times. It was common for subjective relief to precede, or occur in the absence of, objective clearing of pulmonary signs of the asthmatic attack (cf. Case 1). In our analysis of results of khellin therapy (Tables I and II), however, results were not classified as excellent or good unless objective evidence of improvement was shown. Prolonged relief—of at least several hours' duration—was shown by all cases considered benefited by khellin.

Other workers,^{1,4,5} who have used 200 to 300 mg initial doses of khellin in the treatment of bronchial asthma, reported higher percentages of beneficial results than was obtained in this series. Our preliminary investigations, using varying dosages of khellin, suggested that 100 mg single doses might give satisfactory effects with minimal side reaction. This amount

KHELLIN IN BRONCHIAL ASTHMA—DERBES ET AL

was, therefore, selected as the individual dose for use in this study. In some instances repetition of the dose at one to two hour intervals seemed to afford additional relief to patients receiving little or no benefit from the first dose.

No significant changes in blood pressure were produced by khellin. With but one exception all readings were within a range of ± 10 mm of mercury; in this one case an initial pressure of 120/85 fell to 70/50 within one and a half hours, with prompt return to normal levels after the intramuscular injection of $\frac{3}{8}$ gr ephedrine. Since hypotension and shock-like states occasionally occur during acute asthmatic attacks, no conclusion as to possible hypotensive action of the drug can be drawn from this one case. It has been shown, however, that khellin may have a depressing action on blood pressure in the experimental animal; in such instances the effect is transitory.¹⁰

Side reactions in this series included one instance of nausea following oral administration and one after intramuscular injection. Pain at the site of injection was experienced by four patients; three reported headache following the injection. When tablets of khellin were given to private patients (not included in this series), more reported nausea and an occasional patient vomited. In this regard, it is of some historical interest that Mustapha, the discoverer of khellin, recommended its use as an "emetic and narcotic."⁷

CONCLUSIONS

Khellin, in 100 mg doses, relieved a significant percentage (60 per cent) of patients observed during the acute attack of asthma. The drug may be given intramuscularly or orally. Side reactions, which occurred in a low percentage of clinic patients, included injection site pain, headache, and nausea.

One advantage of the administration of khellin is its prolonged duration of action. Also, since khellin has little effect on blood pressure when given in ordinary dosage, it should be particularly useful in asthmatics with concomitant hypertension.

From the results obtained in this series of forty-five patients and from other patients now under observation, it is felt that khellin will have a useful place in the treatment of bronchial asthma.

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(Continued on Page 397)

ERYTHREMIA ("POLYCYTHEMIA") DURING MASSIVE, ORAL, STREPTOMYCES-DERIVED B₁₂ THERAPY

A Report of Two Cases with Further Observations of the "Anti-Allergic" Effects of Streptomyces Fermentation Antibiotics

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P RIMARY erythremia, Osler-Vaquez's disease, is of as yet undetermined etiology. Transition forms such as erythroleukemia and chronic myelogenous leukoblastosis indicate the disease to be a form of myelopoietic hyperactivity, but as in chronic leukemia, no external stimulus to the accelerated hemopoiesis is evident. The term polycythemia is a more accurately descriptive one for Osler-Vaquez's disease because all of the marrow elaborates are increased both in the marrow itself and in the peripheral circulation. Not only is there an overabundance of erythrocytes, granulocytes, and platelets in the circulating blood, but its volume and certain marrow humoral elaborates (cholinesterase, plasma thromboplastinogen, and heparin) are also above the normal level.⁸ The designation of "primary," however, as assigned to this condition may be justifiable only on the basis of the covertness of its etiology and because there are presently recognized "secondary" types of polycythemia in which the cause is overt. Thus, there may be polycythemia which is a compensatory reaction to chronic anoxemia and anoxia. The polycythemia of congenital heart disease, of chronic pulmonary invalidism, and of protracted sojourn at high altitudes are usually cited examples of "secondary" polycythemia. The blood cholinesterase has been found to be increased during residence at high altitudes,¹³ which stresses the possible relationship of this enzyme to hemopoiesis.

Such a relationship between cholinesterase and the activity of the bone marrow has been the subject of considerable speculation.⁷ It may be significant that in chronic allergic states, increased blood cholinesterase concentrations and polycythemia frequently coexist.⁷ This fact has led to the emergence of a third classification of polycythemia, the "reactive" type, numerous examples of which have been studied. It has been contended that the allergic state may evoke a rise in blood cholinesterase as a compensatory mechanism, to assist in the abrogation of harmful antigen-antibody reactions, protecting the organism against the products of such reactions. Since the normoblast manufactures the bulk of the blood cholinesterase, increased normoblastic activity is the result.⁴ Whether or not this contention is a valid one as applied to allergic conditions, it appears to be the reactive cause of a polycythemia in a patient recently studied. In this case, slow protracted bleeding from a duodenal ulcer was accompanied

All materials used in this study were generously supplied by Chas. Pfizer and Co., Brooklyn, N. Y.

by a polycythemia which abated on gastrectomy. The latter point is not clear evidence, for Morris¹¹ has advanced the idea that "primary" polycythemia is due to an excess of "intrinsic factor"—that material which enables the human to absorb "extrinsic factor" (now thought to be B₁₂) taken in with the food. In other words, Morris' concept of polycythemia vera makes it the antithesis of pernicious anemia, in which condition there is a deficiency of "intrinsic factor" so that the ingested B₁₂ (or that synthesized in the patient's gut) cannot be absorbed. Little support in evidence of Morris' theory can be cited. While occasional instances of an elevation above the average normal erythrocyte count for remittent pernicious anemia patients have been recorded, whether this is due to over-treatment with liver extract, or an allergy to the latter, is unknown.

It is of interest in connection with Morris' theory of the etiology of intrinsic or true polycythemia (a theory on which he bases his treatment for the condition) that a transient erythremia developed in two of our patients who were receiving relatively massive quantities of B₁₂ by mouth. The administrations were made as a result of misconceptions entertained by the writers and others that the "animal protein factor" present in streptomycetes broth residues was identical with the B₁₂ which had been crystallized from liver.¹² On the basis of the profound sustentive effect of feeding streptomycetes residue to animals, similar feeding was instituted in a wide category of patients. Some remarkable results, not elicited in these patients by refined B₁₂ administration, were forthcoming.¹ The streptomycetes griseus residue used had been assayed for B₁₂ on the basis of promotion of *Lactobacillus leichmanni* growth, and it was not until much later in our investigations that we realized that only those residues that contained a coliform-suppressor antibiotic were highly effective in patients.⁵ During the interval before the last fact became apparent, several different residues, some from antibiotic-nonproducing streptomycetes strains had been used on patients under the assumption that we were administering a highly potent, "special" form of B₁₂. One of these residues from an antibiotic nonproducer was an oral B₁₂ concentrate assaying 500 gammas/gram. This concentrate, which will be designated as "Oral Grade B₁₂" to distinguish it from other concentrates containing antibiotic (hereinafter designated as "s. griseus residue"), is the subject of the present communication. Oral Grade B₁₂, unlike the s. griseus residue, has never induced nor maintained clinical remission in acute leukemic patients. It nevertheless does possess some physiologic effects, and the present report deals with polycythemia appearing in two patients during its protracted exhibition, under circumstances which lead us to believe that the polycythemic phase was more than casually related to its administration.

CASE REPORTS

Case 1.—A thirty-one-year-old woman with a strong family and personal history of allergy, who for many years had had bouts of giant hives, began to develop

marked pruritus and cough. X-ray examination on February 3, 1950, about six weeks after the onset of her symptoms, revealed a large mediastinal mass. Laboratory examination was negative except for a normochromic anemia, the hemoglobin being 10.2 grams, and a leukopenia with granulocytic shift far to the right. The probable diagnosis was Hodgkin's lymphoma, but we were unwilling to start radiation therapy until this anemia was corrected. She was therefore given injections of B₁₂ and iron cacodylate for a three-week period, when it became apparent that the anemia was not responding and that radiotherapy could no longer be withheld on this basis. At the start of the radiation period, she was given a daily dose of 3 milligrams of oral grade B₁₂. This continued from March 6 to April 11, during which time the patient had received six of an intended twelve fractional doses of x-ray to the mediastinum (dosage unknown). On the last date mentioned she was seen by the writers as an emergency case. Twelve hours previously she had vomited a half cupful of bright red, coagulated blood and again about half an hour before being seen.

On examination at home, one who had seen her five weeks before must have been struck by the alteration in her appearance. She was anxious but not acutely ill. Whereas at the start of radiotherapy (and the oral B₁₂ dosing) she had been very pallid, her face was now definitely flushed, and spider-web telangectases were present on both cheeks. Careful questioning convinced us that this had been a hematemesi; not a hemoptysis. There had been nausea but no coughing prior to both blood expectorations, and the patient, who was rather above the average in intelligence, was sure of this point. She was immediately hospitalized for possible transfusion, and on blood sampling we were amazed to find a hematocrit of .61 with an erythrocyte count of 6.7 millions. The granulocytic spectrum now had a moderate left shift. Transfusion was foregone and the oral grade B₁₂ stopped. X-ray showed the mediastinal mass to have shrunk to one-fourth its original size, and gastrointestinal radiography revealed nothing pathologic. She remained in the hospital, and forty-eight hours after discontinuance of B₁₂ there was a violent attack of giant hives. The patient stated that she had been completely free from them all the time she was taking the material. She was now started on 50 milligrams of terramycin four times daily with milk, which ameliorated the urticaria, and the erythrocyte count declined during her stay in the hospital to 5.3 millions/cu mm. She was discharged on the tenth day on this maintenance dose of terramycin for a resumption of radiotherapy, which was reinstituted on May 14. At the latter time, the terramycin was supplemented with 10 grams of *s. griseus* residue daily (equivalent to 80 gammas of B₁₂).

Radiotherapy was continued until June 21, by which time all mediastinal masses had disappeared and the patient had gained 10 pounds. The terramycin was discontinued and *s. griseus* residue alone given, it being continued to the present time. At the last examination (October 13) the patient was in excellent health, the stool showed a Gram-positive bacillary flora, and the erythrocyte count was 4.3 millions with 12.9 grams of hemoglobin. She has been singularly free from allergic symptoms for the first time in fifteen years.

We believe the bleeding in this case to have originated from an esophageal varix and that the radiation to the chest was not instrumental in its production, although the mucosa of the lower third of the esophagus is radiosensitive. Nor can we attribute the incursion of a distinct polycythemic phase to the x-ray, *per se* (though the senior writer has seen a case of reactive erythremia in an x-ray technician) because the patient had just as much x-ray after, as before the massive B₁₂ dosage was discontinued. We are inclined to attribute the accelerated hemopoiesis to massive B₁₂ dosage and associated factors. One of these associated factors is

an antibacterial substance that differs from the antibiotic found in *s. griseus* residue. It may also be remarked that although *s. griseus* residue and pure coliform suppressor antibiotics have definite corticoid effects in the human, such effects are not entirely absent from B₁₂ concentrates from antibiotic nonproducing streptomyces species. They are merely not so pronounced, nor so constant. Still, in a significant number of instances, we have observed defervescence following administration of oral grade B₁₂ in atypical pneumonia, acute benign lymphosis ("infectious mononucleosis") and rheumatic fever. The latter are definitely atopic reactions, as is also Hodgkin's granuloma.² The pronounced "antiallergic" effect of streptomyces-derived materials promises to make them invaluable in the management of even those atopies which ordinarily take a malignant course.

Polycythemia arising during the course of a patient with Hodgkin's disease cannot be considered part of the evolution of the condition. A similar statement cannot be applied unqualifiedly to the next case, though here too circumstances of the incursion of a polycythemic blood picture likewise tend to incriminate massive oral grade B₁₂ administration.

Case 2.—A fifty-three-year-old office worker, a man, began to fail in weight and strength during the summer of 1949. He had been troubled for years by nightly paroxysms of asthma. In August an abdominal swelling became manifest and this proved to be spleen. Complete peripheral and marrow blood study were conducted elsewhere, and on December 10 he was referred to us with a diagnosis of agnogenic myeloid metaplasia. On the referral date our own examination revealed a markedly pallid, moderately prostrated but cheerful man, who was obviously underweight. The peripheral blood showed 4.05 million erythrocytes, 5.13 thousand leukocytes, with a marked granulocytic shift to the left and many "blast" forms as well as nucleated erythrocytes. Marrow taken from three different sternal sites showed 22 per cent of "blasts," a complete myeloid maturation series, and adequate megalokaryocytes. The diagnosis of "agnogenic" myeloid metaplasia could obviously not be entertained under these circumstances; and even though the spleen was hard and came to the left iliac crest, a diagnosis of subleukemic leukoblastosis, probably subacute, was rendered and a prognosis of from six to eight months of life given. He was immediately started on 15 cc of adrenal cortex extract, aqueous (Eschatin) daily, and this dosage was maintained until January 15, when, though there had been an increase in appetite and sense of well being, it was apparent from the spleen size, the peripheral blood picture, and the continuation of asthmatic attacks, which now became complicated by intense pruritus, that little headway was being made. A course of antihistamines was instituted with some relief to the pruritus, but none insofar as the asthma was concerned. On January 19 the adrenal cortex extract was eliminated except for an occasional (weekly) injection, and he was given instead 2 grams of *s. griseus* residue daily because that residue had already been shown to exhibit pronounced "cortico-therapeutic" effects in other patients.⁶ Be that as it may, the patient stated that his response was gratifying, that the asthmatic attacks were much less severe than at any time in several years, and, indeed, a healthy skin color was manifest for the first time since he had placed himself in our care. Unfortunately, after one week of *s. griseus* therapy, we temporarily ran short of the material, and the cortical extract was resumed in its place. Nightly attacks of asthma recurred within two days after discontinuance of the *s. griseus* residue. On February 2 the adrenal cortex was discontinued and a daily dose of 1000 gammas of oral grade B₁₂ instituted. It was con-

ERYTHREMIA DURING B₁₂ THERAPY—BARNARD ET AL

tinued as the sole medication for one month, during which the asthma and the pruritus completely disappeared. However, toward the end of the month, the patient began complaining of severe abdominal pain which required codeine for its relief and, on February 28, passed a bright red, bloody stool. Examination on March 5 showed a persistent splenomegaly, though one of us thought that there had been some shrinkage. There were markedly dilated capillaries on the face adjacent to the nostrils, along with what appeared to be a marked acne rosacea. The patient's flushed appearance was in distinct contrast to the previous pallor, and the blood study made on this date revealed the reason for the change. There had been a definite hematologic reversion to one of erythroleukemia. The hematocrit was .55 with 5.85 million erythrocytes and 37.4 thousand granulocytes. The spectrum of the latter, though showing a left shift, was orderly. Sternal biopsy revealed merely normoblastic and granulocytic hyperplasia.

The patient stated that since the time of the passage of the bloody stool, he had felt little abdominal pain and was able to work about six hours a day. Because of the freedom from nightly bouts of asthma, he desired to remain on the B₁₂ therapy, about whose "miraculous" effects he had been reading in current popular magazines. We agreed with the continuation of the oral grade B₁₂, although we knew at this time that the effects of other B₁₂-containing residues from streptomyces fermentations, particularly those which were antibiotic producers, were in many instances superior to those to be derived from this particular oral grade B₁₂. The patient was likewise mollified by our statement that the bloody stool was like a nosebleed in acting as a safety valve for excess blood, and B₁₂ was continued until March 22, when the granulocyte count reached 54 thousand, the hematocrit remaining at .55 and the acne rosacea becoming intensified. A daily intake of 10 grams of *s. griseus* residue (representing 80 gammas of B₁₂) was now substituted for the oral grade B₁₂. On April 13 there were 4.13 million erythrocytes, 14.0 thousand leukocytes with a moderate granulocytic left shift, and neither leukoblasts nor nucleated erythrocytes in the peripheral smear. Acne rosacea had disappeared and the only complaints were those of vague abdominal discomfort and recurring pruritus. The *s. griseus* residue was increased to 20 grams daily with some abatement of the pruritus. On May 7 there were 9.2 thousand leukocytes, and the peripheral smear could be pronounced "normal" in all respects. On this date, 1 gram of terramycin was started daily. This dose has been gradually decreased, as it tends to produce, in this patient, stool looseness to the point of diarrhea. He now alternates between mixtures of terramycin and chloromycetin (the latter he believes to be constipating in contrast to the terramycin) and penicillin, which he believes makes him feel perfectly well. On the date of the last examination, October 22, his condition is certainly no worse than when he was first seen a year ago and he has apparently outlived, in relative comfort, the prognosticated span.

DISCUSSION

Erythremia attending massive B₁₂ ingestion may be an example of cobalt polycythemia, first reported by Waltner.¹⁴ The amounts of elemental cobalt ingested by our patients was necessarily small because it comprises only about 1/25th, by weight, of the B₁₂. The difficulty of regarding our cases as specialized ones of cobalt polycythemia disappears if one considers that the mechanism of cobalt polycythemia may be purely one of B₁₂ synthesis, either in the intestinal tract or elsewhere (parenterally administered cobalt is partially excreted into the gut). Barron's hypothesis, that cobalt acted to produce tissue anoxia, through combination with and vitiation of the action of sulphydryl enzymes, and thus impelled the hemo-

poietic marrow to increased activity on an anoxic basis, is not tenable.⁹ Davis¹⁰ has made some excellent physiologic studies of this mechanism, without affording a direct answer, though he was the first to indicate the role of cholinesterase in hemopoiesis. Barnard³ has advanced the idea that B₁₂ is concerned with erythrocyte esterase synthesis. The latter theory furnishes the most adequate explanation, at this time, of why B₁₂, certain orally ingested antibiotics, and the corticoids (corticosteroids and adreno-corticotropins) may have overlapping, duplicating, or identical effects both in the hypersensitivity states and those in which the blood cholinesterase is markedly reduced. The common mode of action of these three distinct substances may be the limitation of circulating proteose. Proteoses ("peptones") directly vitiate cholinesterase activity, and when present in the blood in excess quantities they produce a type of intoxication now explicable on the basis of cholinesterase inactivation. Sources of blood proteose, which may show augmentation in certain morbid states, are believed to be (1) the intestinal tract, where they are produced by the proteolytic activity of certain bacteria, (2) the antigen-antibody reaction occurring in the active allergic state, (3) during tissue autolysis in infections and other morbid processes, and (4) as a result of disordered protein catabolism. If B₁₂ augments cholinesterase synthesis, it could curtail proteose intoxication from any of these sources. The detailed explanation of our theory of the possible action of B₁₂ in this regard is rendered elsewhere.

The two patients on which the report is based have had a variety of treatment with other streptomyces-derived fractions since the discontinuance of the B₁₂-rich material. While they have not been cases of the most rapidly progressing "malignant" dyscrasias encountered and treated by streptomyces-derived materials, an analysis of their response indicates that it was probably better, on the whole, than those to be anticipated by current modes of therapy. The associated allergies in each patient, responding as they did to crude streptomyces-derived materials (and also, in each instance to a streptomyces-derived antibiotic) fortifies a prior impression that the malignant leukoblastoses are atopic in nature. The possibility of abrogating allergic phenomena by the administration of the increasingly available streptomyces-derived materials, points a new direction in the management, both of the definitive allergies and the malignant leukoblastoses.

SUMMARY

Case reports on two patients who developed transient erythremia while ingesting high dosages of streptomyces-derived, crude B₁₂ concentrates, are presented. The ingestion was also attended by a marked abatement of allergic symptoms and a stabilization of a malignant leukoblastotic process, in each instance. The observations are discussed with regard to possible interrelated activity of adrenocorticoids, B₁₂, and certain orally ad-

ERYTHREMIA DURING B₁₂ THERAPY—BARNARD ET AL

ministered streptomycetes-derived antibiotics. It is believed that the anti-allergic, antileukoblastic effects of certain streptomycetes-derived materials may make them valuable in therapeutics.

ADDENDUM

At publication time, both patients are working daily, in good health and being maintained on a daily oral dose of 200 mg. of terramycin. The patient in Case 1 relapsed in February, 1951, with recurrent giant urticaria, cervical adenopathy and a coliform stool. It was discovered that the current lot of *s. griseus* residue was devoid of antibiotic. Prompt remission with as rapid a lymphoid involution as seen during radiotherapy, followed the reinstitution of terramycin and *L. acidophilus* milk.

In Case 2, it was possible to induce a second period of transient polycythemia during March, 1951, by the daily oral administration of 0.4 mg. of crystalline B₁₂.

Subsequently studied cases of leukemia and Hodgkin's disease have shown a salubrious response that could hardly be coincidental to oral terramycin therapy. This response was only forthcoming when intestinal coliform suppression and an odorless stool was maintained. Presumably in these cases, the allergen concerned arose from the intestinal tract; it is designated as an allergen because a hard core of allergy runs through the malignant leucoses (leukemia and Hodgkin's) as ineradicably as Perner and Waldman (*Ann. Allergy*, 8:583-591 (Sept.-Oct.) 1950) have finally demonstrated it to exist in a benign leucosis, so-called "infectious mononucleosis." Examination of the mode of action of streptomycetes-derived materials in these non-infective conditions must take into account, not only their adrenocorticomimetic effects but also the recently elucidated phenomenon that some of these materials, including B₁₂, might have definite androgenic effect, the replenitive and sustentive role of *s. griseus* materials being quite comparable in many respects to those of testosterone.

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COMBINED ALLERGIC AND PSYCHOSOMATIC TREATMENT OF BRONCHIAL ASTHMA

(Continued from Page 329)

ing parents, in themselves insecure and emotionally unstable, themselves the victims of their own neuroses, setting a daily example to their children of retreat from reality, only too often into illness. When we talk of the hereditary factors in allergy we must sometimes wonder whether the child has inherited an inner genetic or an outer neurotic environment. Of the two, in borderline patients, the second may be the more important. In patients who are both allergic and neurotic, we must give no less emphasis to the allergy but much more emphasis to the patient's emotional environment and his responses to it. Only in this way can the patient be treated, as he should be, as a whole person.

When this approach is used, the results are immediately apparent. They are recognized by a simple change in the patient's attitude. The borderline patient shows none of the "resistance" seen in psychoanalysis. When properly treated, he tells you that he looks forward to each new appointment. He comes into the office eagerly and leaves it with regret. Your colleagues may wonder why they never see any of your patients. They may be certain that you hypnotize them. The patient senses that you are not looking at him as a case of asthma but that you identify yourself with him as a whole person. This is the hallmark of good treatment of the borderline allergic and psychosomatic patient.

75 Bay State Road.

MAY-JUNE, 1951

367

ON THE INCIDENCE OF SENSITIVENESS TO CORN

A Criticism of Diagnostic Procedure

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DURING the summer of 1949, an extended hearing on "Bread Standards" was held before the Federal Security Administrator. It included a consideration of the possible allergenic ingredients of bread, including corn and the refined corn derivatives. Testimony, offered by several allergists on August 3 and 4 and on September 19 and 20, 1949, revealed a sharp difference of opinion regarding the incidence of sensitiveness to corn among the allergic population. Two schools of thought gave vent to their respective judgments.

Dr. Theron G. Randolph, as a champion of one school, testified that he had found eighty-seven cases of corn sensitivity in 200 patients suspected of food allergy. This represents an incidence of 43.5 per cent. In the first 100 cases of this series, the feeding test was performed with canned corn or corn meal gruel. In the second group of 100 cases, the addition of corn sugar to the corn meal gruel increased both the incidence and severity of symptoms after ingestion. Later in his testimony, Randolph asserted, "Considering the number of patients studied for food allergy in my office, one out of every five new patients (or 20 per cent) was found to be corn sensitive. . . . Random sampling and general experience during the past two years indicate that these figures are still accurate."

Support of Randolph's finding was furnished by written statements from two physicians. Dr. Michael Zeller of Chicago encountered thirty to forty corn-sensitive patients during the past year. He added significantly: "The incidence of corn sensitivity is present much in proportion to how one searches for it." Dr. Albert Rowe of Oakland reported that he had found 20 to 35 per cent of 1,200 patients allergic to corn. He, furthermore, expressed the view that trial diets or the techniques of Rinkel and Randolph were the only dependable measures in the diagnosis of food allergy.

At the same hearing, dissenting opinions regarding the alleged high incidence of sensitiveness to corn were voiced by Drs. Alan G. Cazort, Lawrence J. Halpin, Frank A. Rawling, John M. Sheldon, and myself. Of special interest is the testimony of Dr. Frank A. Rawling, a former colleague of Dr. Randolph. His study of 1,250 case records revealed fifteen patients with corn sensitivity, indicated either by skin and/or by ingestion tests. In terms of the general population, Dr. Rawling estimated the incidence of corn sensitivity to be 0.03 per cent.

In sharp contrast, also, the findings from a questionnaire, which had been submitted by Dr. Mary H. Loveless to experienced allergists of the coun-

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try, assume significance. Nineteen physicians reported that they had tested within a recent five-year period approximately 35,826 patients for corn meal sensitiveness and that among this number fifty-six cases had been found clinically sensitive to corn, the percentage being 0.12.

Dr. Randolph explains the great disparity in the incidence of corn sensitiveness of 20 per cent as claimed by him and the 0.12 per cent incidence of many other practitioners of allergy. "It is our impression," he postulates in a recent publication,² "that current differences of opinion in respect to the clinical significance of allergy to maize and its products is due in part to the inability of patients and clinicians to avoid its ingestion, and in part to the perpetuation of outmoded methods of specific food diagnosis. In the latter connection, we refer particularly to the mechanical performance of cutaneous and intracutaneous skin tests with food extracts and, to a lesser extent, to the continued use of certain restricted diagnostic diets which do not specifically eliminate certain corn-containing products."

Randolph's condemnation of current "outmoded methods of specific food diagnosis" clearly defines the issue. It, therefore, became a matter of paramount importance to apply the Randolph technique to a study of my patients in order to confirm or disprove the alleged high incidence of sensitiveness to corn. This I have done in a series of fifty cases, and I am unable to confirm the findings which Randolph has reported.

It is to be emphasized that the diagnosis of sensitiveness is based upon the ingestion test only. The limitations of clinical history and of the skin test for the determination of food sensitiveness are now fully recognized and have been disregarded as determining factors in diagnosis in the series under critical study.

There are four stages to the Randolph technique:

1. A period of four days during which the test food is ingested.
2. A succeeding period of four days of abstinence from the test food.
3. The ingestion of the single test food on a fasting stomach the following morning.
4. The observation of resulting signs and symptoms.

Our previous work in the study of alleged cottonseed oil sensitiveness demonstrated the necessity of eliminating the influence of psychic factors. There are many allergic persons who are so sensitized to suggestion that their expressions of food disagreements must be evaluated. Such attitudes are betrayed when in consultation they exclaim, "Why, the very thought of that food makes me sick."

Every effort has been studiously made to avoid these pitfalls in the diagnosis of corn allergy. Accordingly, our subjects were advised to continue with their usual diet during the first stage of the test. The consumption of corn, corn products, and corn derivatives was not stressed lest suspicion be aroused. Randolph's edict, "corn is, by all means, the most difficult food in the American diet to avoid" and "corn is mixed with more foods than any other food" would make any additional encouragement unnecessary.

SENSITIVENESS TO CORN—BERNTON

INSTRUCTIONS FOR FOOD TESTING

It is important that you follow the instructions and adhere closely to the restricted diet for four successive whole days.

You are permitted to select any of the following foodstuffs.

Breakfast:

Fruit:	Any <i>fresh</i> fruit or Dole's pineapple and pineapple juice or Welch's orange and tomato juice.
Cereals:	Instant and hot Ralston Wheatena Cream of Wheat Shredded Wheat Cream of Rice Maltex Pettijohn's Quaker Rolled Whole Wheat Cereal Quaker Puffed Rice Quaker Puffed Wheat Quaker Oats sweetened only with granulated sugar.
Eggs:	Boiled, poached, scrambled or fried in bacon fat, lard or butter. Avoid oleomargarine and vegetable shortenings.
Bacon and Ham:	Only Armour's "Star" Wilson's ham and bacon Swift's "Brookfield," "Oriole" and "Premium ham and bacon."
Ry-Krisp	
Beverage:	Coffee, tea or milk (bottled in glass containers only).

Lunch or Dinner:

Soups:	Only homemade soups, made from fresh vegetables and meat. (No corn or cornstarch is to be used.) Avoid all canned soups.
Meats:	All fresh meats, baked, broiled or fried in their own fat or in lard, butter or bacon fat. Avoid all vegetable shortenings. Poultry, served with no dressing or gravy. Fish, served with no sauces.
Vegetables:	All fresh vegetables, except corn.
Salad:	Fresh lettuce and tomato salad with vinegar and pure olive oil or Wesson Oil dressing.
Dessert:	Fresh fruit only.
Ry-Krisp	
Beverage:	Coffee, tea or milk (bottled in glass containers only). Fresh fruit drinks.

Do Not Eat the Following:

1. Candy and chewing gum
2. Jams and jellies
3. Baker's products: bread, crackers and pastries
4. Alcoholic beverages and all soft drinks
5. All canned, frozen fruits and vegetables
6. All canned, packed and prepared meats: Spam, Armour's Ham or Treet, Swift's Prem, frankfurters, sausages, bologna, and lunch ham
7. All dry cereals except Quaker Puffed Rice, Oats and Wheat and Shredded Wheat
8. All fried foods, except those fried in bacon fat, butter or lard
9. Oleomargarine
10. Powdered sugar
11. Corn—fresh, canned or frozen
12. Corn meal and all food prepared with it such as Fritos and popcorn (Note food labels)
13. Corn starch and all foods prepared with it
14. Corn oil (Mazola) and all salad dressings and foods which may contain it
15. Table syrups (Karo) and other syrups made of corn syrup or dextrose
16. All gravies and sauces of unknown ingredients
17. Jello, puddings and ice cream
18. All canned soups
19. Wheat flour and all foods containing it
20. Salt: in salt cellars as made available in public eating places

SENSITIVENESS TO CORN—BERNTON

In Addition Be Careful to Avoid the Following:

1. The use of paper plates or cups
2. The occasional snack away from home such as a sandwich
3. Fried foods as served in public eating places
4. Any canned foods

REPORT SHEET

Name:

Address:

Begin the restricted diet on _____
with it for four successive days.

and continue

On the morning of the fifth day:

1. Do not take any food or drink
2. Do not take any medicine
3. Do not smoke

You will please report at my office at _____ A.M., on _____
clinic

	First Day	Second Day	Third Day	Fourth Day
Date				
Breakfast				
Lunch				
Dinner				
Symptoms				

The soundness of this edict was, furthermore, verified by the sheet of Instructions for Food Testing which was issued to each patient preparatory to the ingestion test. The instructions to my patients were based on a pamphlet written by Dr. H. J. Rinkel, entitled "Corn, a Brief Description of Clinical Importance, Edible Forms, Modes of Exposure and Common Sources of Contact."

A perusal of the instructions, especially the paragraph on the second page, under the heading "Do not eat the following," clearly indicates the extent of the sacrifice of the abundant life which my patients willingly made. A report sheet was also issued with the Directions for Food Testing in which the patient recorded the articles of foods ingested while on the restricted diet during the four-day period. This record served a twofold

SENSITIVENESS TO CORN—BERNTON

purpose. First, it made the patient diet-conscious and proved to be a constant reminder of his obligation. Secondly, it enabled me to check how faithfully each patient adhered to the restricted diet and the completeness with which corn was eliminated during the trial period. A report of symptoms for each day of the trial period was also highly instructive. A continuation or aggravation of complaints while on the corn-free diet suggested other possible etiologies.

My series consisted of fifty patients, of whom fifteen were males and thirty-five were females. They were selected from private and clinic practice. Twenty-four patients represented new admissions, and twenty-six were patients who had been under my care for one year or longer. Both Dr. Randolph and Dr. Rinkel catalogued the incidence of corn sensitiveness in "consecutive cases." My new admissions, other than uncomplicated seasonal hay fever victims, were likewise "consecutive cases," whereas the older group was comprised of patients with various allergic manifestations whose skin tests or clinical history suggested corn allergy.

All the cases had been previously screened by their physicians before referral to me for an allergic study. As part of the routine, tests for protein sensitization were performed with epidermal and miscellaneous proteins, with representative pollens of our local flora and with molds for the detection of inhalant allergens.

Table I indicates the grouping of patients according to symptoms, as well as their sex, age, and duration of disease.

The summary is as follows:

Asthma	22 cases
Asthmatic bronchitis	6 cases
Vasomotor rhinitis	3 cases
Hives	4 cases
Pruritus	2 cases
Perennial hay fever	2 cases
Hay fever and eczema	1 case
Hay fever and asthma	2 cases
Hay fever, asthma, and headache	1 case
Hay fever, asthma, and eczema	1 case
Asthma and eczema	1 case
Asthma and angioneurotic edema	1 case
Asthma and gastrointestinal allergy	1 case
Eczema	1 case
Stomatitis and glossitis	1 case
Headache	1 case
Total	50 cases

On the morning of the ingestion test, the patients reported at the office or clinic after having been previously admonished not to smoke and not to take any food, drink, or medicine prior to the test. They were then kept under observation for one-half hour. During this control period, certain physical findings and symptoms were noted and recorded. These included pulse, respiration, blood pressure, vital capacity, asthma, coughing, sneezing, coryza, itching, goose flesh or chilling, yawning, stretching, rubbing of

SENSITIVENESS TO CORN—BERNTON

TABLE I. ANALYSIS OF CASES SUBJECTED TO INGESTION TEST WITH CORN

Disease	Sex		Age	Duration	
	Female	Male	Years	Years	Months
Asthma	x		39	10	
	x		58	16	
	x		26	24	
	x		57	19	
	x		39	35	
		x	41	12	
	x		31	10	
		x	25	25	
		x	22	20	
	x		53	30	
		x	49	3½	
	x		42	22	
	x		30	2	
	x		37		1
		x	12	6	
	x		34	4	
		x	33	28	
	x		44	19	
		x	21	18	
	x		47	6	
	x		14	13	
	x		48	22	
Asthmatic bronchitis	x		38	10	
	x		33		10
		x	15	6	
		x	46	44	
	x		23	16	
		x	15	7	
Vasomotor rhinitis		x	36	10	
	x		48	15	
	x		40	20	
Hay fever and eczema	x		47	2	
Headache	x		27	1	
Hives	x		22	2	
	x		21		9
		x	35	1	
	x		43		3½
Eczema	x		36	10	
Pruritus	x		44	2	
		x	54		6
Asthma and eczema		x	19	17	
Stomatitis and glossitis	x		52	3	
Asthma, angioneurotic edema	x		38	7	
Asthma and gastrointestinal allergy	x		49	37	
Hay fever and asthma	x		37	17	
	x		42	15	
Hay fever, asthma and eczema	x		21	19	
Perennial hay fever		x	14	3	
	x		37	10	
Hay fever, asthma and headache	x		34	8	

neck, diarrhea, fatigue, hives, headache, eczema, gastrointestinal ailments and other signs and symptoms.

Each patient was then given a jar containing 4 ounces of warm corn meal mush and requested to eat it. It is to be emphasized that the patients were not advised of the nature or source of this food. The patients were kept under close scrutiny for the development or aggravation of clinical symptoms. At twenty-minute intervals during the hour after the feeding,

SENSITIVENESS TO CORN—BERNTON

Symptoms and Physical Findings	Half-hour Control Period Time Begins	First Feeding Time Begins			Second Feeding Time Begins		Date Name Diagnosis Ingestant	No.
		0-19	20-39	40-60	0-14	15-30		
Pulse							Comments and Impressions	
Respirations								
Blood Pressure								
Vital Capacity								
Asthma								
Coughing								
Shneezing								
Coryza								
Itching								
Goose Flesh-Chilling								
Yawning								
Stretching								
Rubbing of Neck								
Diarrhea								
Fatigue								
Hives								
Headache								
Eczema								
Gastrointestinal								
Other								
							Follow up	

SENSITIVENESS TO CORN—BERNTON

determinations of pulse, respiratory rate, and blood pressure were made. These and other physical findings and symptoms, if any, were recorded on a special sheet.

If there were no signs and symptoms at the end of the hour to indicate a clinical sensitiveness to the corn meal mush, a second feeding of 4 ounces of the mush was given. The patients were held under observation for an additional half-hour. Before the patients left the office or clinic, they were instructed to continue with their restricted diet for the rest of the day and to note any delayed symptoms. These were included in the record of each case and evaluated.

In my series of fifty subjects, two patients exhibited reactions which justified the diagnosis of clinical sensitiveness to corn. One patient, a male, aged thirty-six, had suffered from a vasomotor rhinitis for ten years, and the other patient was a female, aged forty, who had had a similar disability, at varying intervals, for twenty years.

Interestingly enough, the reaction was delayed in the first patient until the afternoon, when he experienced a complete nasal blockage and some sneezing. The ensuing symptoms were more severe than usual. One week later after another corn-free diet of four days, he ate four ounces of corn starch pudding on a fasting stomach. As in all of our ingestion tests, the patient was not aware of the nature of the test food. There were no untoward signs and symptoms observed and reported. The control ingestion test with a corn derivative was clearly negative.

The second patient experienced a "slight burning sensation in the pit of the stomach" after eating the first dish of corn meal mush. This persisted during the half-hour after the second dish of the meal. Later in the afternoon, the burning sensation became more aggravated and tightness of the nose and throat appeared. As the evening wore on, the distress became more acute because of the stuffiness of the nose, tightness of chest and coughing. Sleep was intermittent. On awakening, stuffiness of nose persisted. Twenty-four hours after the ingestion test, an itching papulo-vesicular eruption covered large areas of the body surface—especially the face, arms, neck and scalp. A sense of weakness and headache accompanied the catarrhal symptoms. Follow-up studies of this patient were made in my office during the week following the ingestion test.

A very significant question now presents itself: "What are the criteria of a specific allergic reaction to the ingestion of foods including corn meal mush?" According to Randolph, coughing is the most common symptom and the subjective report of headache ranks second in importance. Other manifestations of a positive reaction include nasal symptoms, such as nasal congestion, sniffing, sneezing, clearing of the throat, itching of the skin—especially under the chin or of the nose—and doubling or tripling in the incidence of minor symptoms, such as the sensation of pulling, drawing tightness in the back of the neck, chilling and goose flesh, objectively measurable. To this list of symptoms, Randolph adds abdominal pains and

cramps, occasional diarrhea, vomiting, tachycardia, and perspiration. He also emphasizes fatigue as pathognomonic of food allergy.³

I join Rawling in dissenting from Randolph's interpretation of the foregoing symptomatology. It is to be noted that allergic diseases are characterized by their chronicity. Accordingly there are periods of freedom from symptoms and periods of acute exacerbations which may or may not be beyond control. Moreover, the mere elimination of a test-food under experimental conditions, even if proved to be later an offending one, does not necessarily free the subject of all food-allergic phenomena. These phenomena, according to my concept, comprise asthma, hay fever, perennial nasal allergy, eczema, urticaria, selected types of headache and gastrointestinal disturbances. The symptoms are, of course, determined by the affected "shock organs." Under the stress of antigenic stimulation, a response from the same "shock organs" is inevitable either as a provocation of acute and characteristic symptoms or an aggravation of residual symptoms.

I do not regard the minor symptoms which Randolph has enumerated, such as the sensation of pulling, drawing tightness in the neck, stretching, and fatigue as diagnostic of a specific allergic reaction to the ingestion of a test-food. In my two positive cases of the series under investigation, there was an unmistakable reproduction of the symptoms which constituted their malady. Some of the minor symptoms which Randolph enumerated were observed in my patients—even during the first-half hour, prior to the ingestion test. Coughing was by far the most common symptom, both before and after the ingestion of the test-food; and in four subjects, musical râles were present during the control and test periods. Fatigue was an infrequent complaint, although four patients fell sound asleep.

There is one phase of food allergy which invites attention at this time, namely, its tendency to be multiple. According to Rinkel,⁴ the number of foods to which one becomes sensitive increases with age—in asthma, the average is above ten per patient. Rinkel is also author of the phrases "masked food allergy" and "masked or chronic smoldering reaction." The terms are applied to the symptoms which develop after a delay of several hours, especially in the morning, after the ingestion of meals containing the specific allergenic food.

In the Randolph technique, there is an omission of one test-food for a period of four days. There is no restriction in the use of other foods. In the study of new cases in which corn is employed as the test-food, the consumption of basic foods such as wheat, milk, egg, potato, orange, beans, beef, tomato, coffee, lettuce, and pork is indispensable in the diet of the average person. These are the very foods which Randolph lists in the order of incidence which cause masked allergic reaction. On the morning of the fifth day, the single test-food is ingested on a fasting stomach. It is conceivable, therefore, that the minor symptoms which ensue can be at-

SENSITIVENESS TO CORN—BERNTON

tributable to the masked or chronic smoldering reaction of other foods ingested during the preceding four-day period.

It is noteworthy that there has been a serious omission of the influence of climatic conditions upon patients on the morning of the test. Exposure to cold outside air, rainy and damp weather, and snowfall have a deleterious effect upon the asthmatic state.

Patients come to the office or clinic from afar by automobile or in crowded buses or street cars. They have had no food, no drink, and no medication. Their normal mental and psychic reactions are disturbed in anticipation of the test. The night may well have been a sleepless one. They sit in the office for two hours, staring at each other and watching closely each move of nurse and physician—some with suspicion and others with confidence. They grow weary and stretch and even fall asleep.

The resulting fatigue is a physiologic reaction. We must give heed to the warning note sounded by Prickman, several years ago: "The attempt should not be made to explain as allergic all diseases or symptoms of an allergic individual. The allergic patient may have bunions, gallstones, hypertension, nervous dyspepsia or psychoneurosis just as the nonallergic individual may have them."

Randolph and Yeager² in a recent publication not only re-emphasize the high incidence of corn sensitivity but also incriminate some of the refined corn derivatives as allergenic offenders. In the treatment of corn allergy, they recommend the elimination of cornstarch, corn sugar and corn syrup—which are omnipresent in the American diet. They even urge a careful investigation of the current widespread use of corn syrup in infant feeding, implying thereby that corn syrup may become a sensitizing factor in infancy. If 20 per cent of the allergic population is sensitive to corn, as claimed by Randolph, it follows that a considerable segment of our patients is to be denied the enjoyment of an important food and its derivatives. This study and the experiences of other allergists which I have reported fail to confirm such a high incidence of patients sensitive to corn.

Randolph's findings are five times greater than mine, even though mine are obtained with the employment of his technique. This glaring difference is as distressing as it is challenging. The question "Why this difference?" comes to the mind of all physicians interested in the diagnosis of food allergy. Is Randolph's syndrome of food allergy valid? The welfare of our patients is very much involved in these questions. The answer can be readily obtained by following a practical and simple procedure. A pattern for the procedure was established by Bernton, Coulson and Stevens in their study of alleged sensitiveness to cottonseed oil.¹ The "blindfold" test which they have described may well be applied to the diagnosis of corn allergy. I, therefore, recommend the appointment of a "verification committee." This committee will be charged with the responsibility of submitting

(Continued on Page 386)

MECHANISM OF ALLERGY OF THE EYE AND ADNEXA

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DURING the last ten years, due to the research and writings of Le-moine, Bothman, Woods, Ruedemann, Hansen, Hanser, Gill, Duggan, and others, there has developed an increasing interest in allergy in the practice of ophthalmology, and as a result, the symposium chosen for the last meeting of the Academy of Ophthalmology and Otolaryngology was on "Allergy of the Eye, Ear, Nose and Throat."

CONCEPTS OF ALLERGY

No other subject in the whole realm of immunology is more confused by a multiplicity of terms than that commonly designated as anaphylaxis. "Without protection" (Richet's definition of allergy), "altered reactivity" (von Pirquet), "strange disease" (Coca), "protein sensitization" (Vaughan), "toxic idiopathies" (Freeman), "cellular immunity" (Metchnikoff),⁸ "local hypersensitive reaction" (Arthus and Breton), as well as "hyperergy," "protein hypersensitiveness," or "idiosyncrasy," have been terms used to designate the allergic reactions.

This diversity of terminology is not to be wondered at when we consider our present relative ignorance of the complex mechanisms concerned, the frequency of the protean clinical manifestations, and the difficulties that hamper our elucidation of its mysterious nature on account of a multiplicity of causes and paths of introduction. The whole source of this confusion would seem to be in the essential lack of harmony between earlier classifications and later developments in our knowledge.

During the last thirty years the general concept that humoral antibodies must be present in all allergies has been held by many allergists and immunologists, although they have not always been able to find them; evidently there are other factors present.

Duke,⁶ in 1925, pointed out that the majority of individuals with allergic symptoms fell into a group in which no significantly positive results with skin tests could be obtained. These individuals Duke found to be sensitive to physical agents such as temperature changes, fatigue, changes of atmospheric pressure, and also emotional perturbations. He noted that these reactions could involve an area, a tissue or an organ, and he suggested that in many of them a reflex acting through the autonomic nervous system released the H-substance of Lewis. Peterson¹³ has written extensively along the same lines.

Cannon and Pacheco also felt that the "humoral" hypothesis of allergy

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ALLERGY OF THE EYE AND ADNEXA—POOS

left something to be desired. They stated that the relatively unsatisfactory results of many years of emphasis on humoral factors in the defense against infectious disease have gradually led to a re-examination of some of the underlying mechanisms involved, and, as a result, the cellular reactions of immunity are now receiving more attention. They called attention to the accumulating evidence that antibodies are probably formed in the cells of the reticuloendothelial system, in a large part at least, and suggested that the circulating "humoral" antibody might be considered a mere by-product of developing immunity in these cells.

Kahn introduced the concepts of tissue immunity. He rejected the suggestion that specialized cells would be entrusted with the entire defense of the body, but thought it would be reasonable to suppose that all cells possessed in some measure the ability to defend themselves against environmental stress, whether such stress presented itself in the form of invading organisms or in some other forms. He felt that immune gamma globulin should be considered of two types: one which must be considered insoluble because it remained fixed in the cell, the other which could be considered soluble because it is dissolved into the blood serum to form circulating antibody.

Kahn embraced the "unitarian" theory of Zinsser, Enders and Fothergill, in which sensitizing antibody, opsonin, agglutinin, blocking antibody, and the like can be considered to represent varied physiochemical changes in the same globulin. He felt that "allergy" was merely an instance of hyperimmunity and stated that in physiology there were many examples of overaction of a physiologic mechanism. Kahn defined an allergic individual as one who develops immunity more readily to smaller quantities of an antigen than does a normal individual, who develops immunity to substances to which a normal individual would not become immune, and who reacts more violently than would a normal individual to a given quantity of antigen.

CHEMISTRY OF ANTIGENS

The majority of antigens are proteins, although certain polysaccharides are known to possess antigenic activity. Polysaccharides and proteins show striking chemical resemblances in their colloidal properties, chain structures, and polar acidic and basic radicals; most native proteins are actively antigenic. Insulin, Warburg's yellow enzyme, and the crystallin of serum are rather ineffective. Antigens and such low molecular preparations as albumoses, gelatin protamines, and proteoses have very feeble antigenic activities. However, proteins with low molecular weight can, at times, be transformed into very active antigens by coupling them with substances called haptens. To function as an antigen, a protein must be capable of forming a suitable colloidal solution. Thus, heat-coagulated proteins are antigenic only if they can be redissolved.

There are striking phylogenetic relationships between natural antigens:

for example, the serum proteins of man and anthropoids are more closely interrelated than are the serum proteins of distant species.

Other proteins which show phylogenetic relationships are the globins, pepsins, egg and milk proteins, and globulins of brain, muscle and other organs. By contrast, the amyloids, insulins, keratins, lens globulins, thyroglobulins, and flavoproteins of different species are less differentiated. Their small species differences are overshadowed by a powerful radical common in all species to each of these proteins.

The interrelations of antigens are due partly to the chemical patterns of the proteins themselves. They are also tremendously affected by combination with prosthetic radicals, such as polysaccharides, lipides, and polypeptides, and by the introduction of chemical radicals by oxidation (to oxyprotsulfonic acids), nitration (to colored anthoproteins), halogenation (to iodoproteins and bromoproteins), halocompounds (to colored azoproteins, denaturation (nitramolecular rearrangement), methylation, acetylation, and sulfonation.

ANTIBODIES

The circulating antibodies are modified serum globulins. Their formation, during immunization, frequently causes an increase in globulin concentration of the serum. The formation of antibodies depends on structural differences between the antigenic protein and the protein of the host. The cell proteins are, in other words, coenzymic templates which specifically direct the synthetic reactions.

There is much evidence to suggest that the reticuloendothelial cells are the chief sources of circulating antibodies in animals. In mammals, the liver is probably an important site of antibody synthesis, since this organ is one of the chief sources of normal serum globulins.

The combination of antigen with antibody is a colloid chemical reaction of marked specificity. Specific flocculates produced in the immune sera absorb appreciable quantities of salts and lipides, but do not contain specific proteins capable of absorptive and electrostatic phenomena, but are merely accessory factors to the specific immune reaction. The individual living cells possess the mechanism for antibody formation. Tissues can also assimilate circulating antibodies from the blood stream.

Infections usually begin as localized inflammatory processes, which stimulate defense mechanisms in the tissues. Even after the infectious organisms have gained access to the blood stream, they are abundantly exposed to the activities of endothelia and leukocytes. Hence, the circulating antibodies are only secondary factors in tissue immunity.

HYPERSENSITIVITY

Conditions of abnormal sensitivity to antigens and haptens are widespread in animals and man. They include anaphylaxis and anaphylactoid allergies and idiosyncrasies. The cardinal symptoms resemble those pro-

duced by the injection of histamine or proteoses. They are referable largely to stimulation of smooth muscle and to increased capillary permeability with marked transudation of plasma proteins into the tissues. Epinephrine, ephedrine and antihistaminic drugs tend to counteract these effects, and they are used clinically to provide temporary relief from anaphylactoid symptoms. The combination of antigen with its specific antibody *in vivo* induces rapid liberation from the tissues of a toxic anaphylatoxin which is either histamine or a closely related substance. Histamine is regarded as the anaphylatoxin, even though certain organs and species appear to be resistant to its action, and heparin inhibits anaphylactic shock but not histamine intoxication.

The anaphylatoxin originated from the tissue precursor (not from the provocative antigen). A most minute quantity of foreign protein can elicit anaphylactic shock in the sensitized animal. Excised tissues exhibit the same hypersensitivity as the intact animal. Anaphylatoxin or histamine is liberated most readily by the hypersensitive liver, lung, intestine, and kidney, and less extensively by hypersensitive brain, skin, and spleen, when isolated tissues are incubated with the specific antigen.

ANAPHYLAXIS

True anaphylaxis results from the parenteral introduction of a specific antigen into a sensitized animal. An initial injection of the antigen, even in exceedingly minute dosage, induces a state of hypersensitivity which develops gradually during a period of from one to three weeks. The second injection of the same antigen (or its corresponding hapten) following accumulation of the serum antibody, induces a violent anaphylactic response. Human beings are less susceptible to these effects than are most laboratory animals. The chief symptoms of clinical anaphylactic shock are pruritus, urticaria, erythema, cyanosis, coughing, dyspnea, edema, weakness, and coma. Skin allergies include urticarias, eczemas, and certain angioneurotic edemas which are caused by drugs, chemicals, cosmetics, animal furs, foods, and plant substances. Intradermal skin tests are most useful in the urticarial and erythematous allergies, while patch tests are more useful in the exanthematous types. The drug idiosyncrasies represent haptenic immune reactions, usually manifested by skin allergies. Anaphylactoid drugs either combine with tissue proteins to form foreign antigens *in vivo*, or they cross-react with normal tissue constituents in susceptible individuals.

The typical anaphylactoid drugs contain such chemical radicals as aromatic nuclei, arsenic, loosely bound nitro or halogen radicals which combine readily with proteins, antipyrine, arsphenamine, atropine, bromides, cocaine, novocaine, quinine, salicylates, aspirin, and penicillin, and are common causes of anaphylactoid symptoms. Skin allergies and drugs affect the eyelids. Bacterial allergies may occur during such infections as gonorrhea, pneumonia, rheumatic fever, syphilis, and tuberculosis, but may be

ALLERGY OF THE EYE AND ADNEXA—POOS

due to other infections, as well as virus and fungus infections. These allergic states are caused by sensitization to bacterial antigens.

These reactions result in various allergic manifestations of the lids, conjunctiva, cornea, iris, lens or retina.

1. *Lids*.—Edema, external dermatitis, contact dermatitis, eczema, blepharitis, secondary lesions as chalazia, hordeolum.

2. *Conjunctiva*.—Acute allergic conjunctivitis, hay fever, cosmetics, drugs, chronic blepharoconjunctivitis with eczema, chronic follicular, phlyctenular, often of a scrofulous tuberculosis type. Vernal conjunctivitis, probably pterygiums as a result of sunlight and dust.

3. *Cornea*.—(a) Superficial, acute keratitis, edema, vesicular, phlyctenular, vernal keratitis; (b) interstitial, congenital lues, and tuberculous keratitis.

4. *Iris*.—Iritis due to bacterial allergy, but may be affected by foods, and uveal pigment.

Sympathetic ophthalmia due to pigment sensitization.

6. *Lens*.—Cataract occurring with neurodermatitis and eczema. Also may be anaphylactic due to lens protein.

7. *Retina*.—Some cases of edema, separation of retina and papillitis.

Epiphora due to edema of walls of sac and duct may be caused by foods.

There are quite a few affections of the eye which do not meet the typical antigen-antibody reaction, but are more of a catabolic reaction characterized by vasospasm with secondary dilation of the capillaries and edema.

Muller⁹ (1922) described the vasoneurotic constitution, characterized by the great lability or neurovegetative instability of the innervation of the vascular system which manifests itself in capillaries as well as arteries. Frequent changes in the innervation occur either "spontaneously" or from trivial causes. In the case histories given by Parrissus,¹² it is mentioned how the fingers of certain patients become sometimes white (simultaneous contraction of arteries, capillaries and venules), sometimes strongly red (dilation of all vessels), or deep blue (contraction of arterioles with dilation of capillaries and venules).

Ricker¹⁴ stated in 1927 that the underlying mechanism of hypertension and inflammatory conditions is a neurovascular defect. Various stimuli cause a constriction of all terminal vascular segments (arterioles).

The capillaries become fatigued and relax as after a dose of adrenaline with constricted arterioles and dilated capillaries; there is slowing of the blood stream in the capillary bed. The capillaries next become more permeable, as a result either of lack of oxygen or of opening up of spaces in the capillary walls, depending on the degree of increased capillary permeability, the type of transudate, and the degree of slowing of the blood stream. Ricker differentiated three stages: (1) prestasis or liquor stasis, in which plasma (and fibrin, if inflammatory) are found in the transudate,

(2) peristasis or leukostasis, in which white cells (chiefly lymphocytes) also pass into the perivascular tissue, and (3) stasis or rubrostasis, in which erythrocytes pass through the capillary walls. Therefore, in its simplest forms it must be apparent that prestasis causes edema or urticarial lesions; peristasis causes perivascular edema with round cell infiltration, i.e., periarteritis nodosa; and stasis results in purpuric lesions.

Moon¹⁰ stated that suitably large doses of epinephrine will produce a condition of circulatory failure indistinguishable from shock. Epinephrine may produce maximal arterial constriction of such degree that the tissues suffer from anoxia. If the lack of oxygen is of sufficient duration and degree, atony of capillaries and venules will develop in the area affected. Moon also said that many phenomena called toxic are essentially anoxic. Allergy must be included in these phenomena.

Harkavy⁸ emphasized the role of blood vessels in bronchial asthma with these words: "Since, therefore, the blood vessels appear to be the primary site of the allergic reaction, it may be reasoned that any structure in the body may become a shock tissue if the blood vessels supplying it have become sensitized." He also mentioned the property of histamine-like substances in initiating smooth muscle spasms and increased capillary permeability. He stated that hemopoietic tissues also participate in the generalized allergic response and that the bone marrow may be regarded as a shock organ which may react under allergic stimulation by multiplication of its cellular elements or by suppression.

Muller,¹¹ in 1939, showed that certain individuals have an inherited tendency, on exposure to certain stimuli, to have involvements of the arteriolar and capillary beds, causing a spasm of the arteriole with dilatation and increased permeability of the capillary bed with resulting anoxia, which further increases the permeability, but, as Brown observed, may also have destruction of leukocytes in the capillary loop.

Code⁴ has shown that in the human being most of the histamine in the body is contained in the leukocytes, thus increasing the vicious cycle and producing the typical allergic wheal.

Selye¹⁵ has described the general adaptation syndrome which will probably give us a new concept of many diseases. He uses the term *stress* to include shock, trauma, infections, cold, burns, x-ray, and nervous stimuli to set off a chain reaction affecting many endocrine glands, but especially the adrenal cortex, as well as blood vessels, blood et cetera. He divides it into three stages:

1. The alarm reaction is defined as the sum of all nonspecific systemic phenomena elicited by sudden exposure to stimuli to which the organism is quantitatively or qualitatively not adapted. Some of these phenomena are only passive and represent damage or "shock" (e.g., hypothermia, hypotension, hemoconcentration, increased capillary permeability, hypochloremia, depression of the nervous system); others are manifestations of

active defense against shock (e.g., adrenal cortical enlargement, increased corticotrophin, and corticoid production). Usually the alarm reaction evolves in two phases, the phenomena of shock being followed by those of countershock.

2. The stage of resistance is defined as the sum total of all nonspecific systemic reactions elicited by prolonged exposure to the stimuli to which the organ has acquired adaptation. The impression is gained that during the stage of resistance, adaptation to one agent is acquired at the expense of "resistance to other agents."

3. The stage of exhaustion represents the sum of all nonspecific systemic reactions which ultimately develop as the result of very long exposure to stimuli to which adaptation has been developed, but could no longer be maintained.

Homeostasis (Cannon)³ is the tendency of living organisms to maintain a steady internal equilibrium, that is, to preserve an unchanging *milieu interieur*, as the great French physiologist, Claude Bernard, termed it. It is due to these homeostatic mechanisms that the blood sugar tends to remain constant in spite of continuous glucose combustion or exogenous glucose administration. The maintenance of body temperature despite changes in the temperature of the surrounding medium, and maintenance of a constant blood volume after hemorrhage or intravenous fluid administration, are other examples of this phenomenon.

Williams,¹⁶ discussing the phylogenetic viewpoint, says that when the organism was unicellular or consisted of relatively few cells, the physicochemical changes occurring at the cell membranes or in the tissue fluids were sufficient to re-establish equilibrium. It suggested that as the cellular development became more complicated, the hormonal system developed to speed up these necessary biochemical changes, as certain cell groups became specialized in their function and organs began to develop; and the autonomic nervous system was evolved when localization of effect was found necessary.

It should be realized that the three components of the autonomic system are functionally inseparable physicochemical changes at the cell membrane and in the tissue fluids, influencing both hormone production and autonomic nervous transmission. Hormones influence both the physicochemical changes and the autonomic nervous system. The autonomic nervous system influences both physicochemical activity and hormone production.

The eyeball is a prolongation of the brain composed of ectoderm and mesoderm. It is a vascular organ with a terminal blood supply. It is richly supplied by the parasympathetic and sympathetic nervous system. Therefore, it is subject to many of their imbalances, particularly of neurovascular origin. Some of the most common are:

1. *Cornica*.—Edema, vesicle formation, herpes of cornea, herpes zoster ophthalmicus, some types of ulcers.

ALLERGY OF THE EYE AND ADNEXA—POOS

Some forms of iritis, especially the granulomatous type which may also involve the ciliary body and choroid.

Primary glaucoma, some cases of congestive glaucoma.

Sudden paralysis of extraocular muscles, due to paralysis of cranial nerves of vascular origin.

2. *Retina*.—Angiospasm, edema, thrombosis of arteries and veins, some cases of detachment.

3. *Optic nerve*.—Retrobulbar neuritis, optic neuritis, atrophies of nerve, secondary to angiopathy of blood supply.

Scleritis and episcleritis may be of the rheumatic, granulomatous or periarteritis nodosa type of vascular reaction.

4. *Choroid*.—Acute exudative choroiditis may follow spasm of retinal or choroidal arteries of both, causing a retinal choroiditis.

Neuralgias about the head are often due to vasospasm.

Migraine may be accompanied with spasm of the retinal artery, paralysis of ocular muscles and scotomas, with probable spasm of cerebral arteries, and with probable secondary dilation, especially of capillaries with increased permeability. The most effective treatments are those which (1) paralyze the sympathetic vasoconstrictors, (2) actively dilate arterioles, or (3) supply pure oxygen, which is antagonistic to histamine. Migraine may be due to food allergy, but most of these patients have a vasospastic constitution, are under more or less tension, and have a tendency to be perfectionists. The attack may be brought on by a conditioned reflex from anxiety.

CONCLUSIONS

Allergy is a problem involving immunochemistry, physical chemistry of cells, biochemical imbalances, neurovascular physiology, coenzyme systems, endocrine imbalance, and especially imbalances of the autonomic nervous system. One of the main shock organs is blood vessels, stressed by Duggan.⁵ There is also a large psychosomatic factor in many cases.

By a better understanding of the mechanism of allergy, we are able to treat our patients better. The ophthalmologist has an advantage in being able to see these reactions with the slit lamp and the ophthalmoscope.

The typical allergic reaction of the antibody-antigen type is a defense reaction, anabolic in type with parasympathetic predominance. These cases are helped by stimulation of the sympathetic by adrenaline, by antihistaminic drugs, by desensitization, and at times by foreign protein injections.

The other group, primarily vasospastic, are characterized by a catabolic reaction and stimulation of the sympathetic nervous system. They are helped by vasodilators, sedation at times, building up defenses by cortical extract, ascorbic acid, vitamins of the B group, liver, iron, histamine, amino acids, rutin, and heparin, according to the condition present.

ALLERGY OF THE EYE AND ADNEXA—POOS

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ON THE INCIDENCE OF SENSITIVENESS TO CORN

(Continued from Page 377)

samples of corn meal and other meals as "unknowns" for ingestion tests. Under these circumstances, the results obtained by the allergists whose incidence of corn sensitiveness places them in the higher brackets should prove of inestimable value in the diagnosis of food allergy.

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TREATMENT OF HYPERSENSITIVE RHINITIS AND OTHER ALLERGIC DISEASES WITH CHLOR-TRIMETON

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WHILE there are numerous antihistaminic drugs available for the treatment of allergic disorders, it seemed of interest to investigate one of the more recently introduced members of this group. Chlor-Trimeton, brand of chlorphenylpyridamine maleate,* seemed particularly worthy of study since it has been reported to have a high therapeutic index and low toxicity in animal and man.^{3,5}

Clinical efficacy has also been well established.^{1,2,4,6} It has the advantage of producing relief with doses about one-tenth that required for other antihistaminic drugs on the market.

METHOD

One hundred and one patients were chosen from private and clinic patients, ages ranging from thirteen months to forty-eight years. Thirty-three patients were under fourteen years of age, the remainder being in the adult group. As many of these patients had been under my care for prolonged periods of time, their response to previous medication was known; they therefore served as their own controls. Most of the patients in this study were suffering from seasonal allergic rhinitis; but other allergic diseases were also included, such as urticaria, asthma, nonseasonal rhinitis, and migraine.

In view of the young age of many of the patients, some were started on doses as low as 1 mg of Chlor-Trimeton three times daily. In general, however, the adult patients received 4 mg t.i.d.

TABLE I

Diagnosis	Number of Cases	Results		
		Excellent	Good	Poor
Hay fever	77	48	26	3
Asthma	7	3	2	2
Urticaria	7	7
Rhinitis	5	2	1	2
Migraine	1
Miscellaneous	4	..	3	1
Totals	101	61	32	9

RESULTS

Hay Fever.—Results obtained are summarized in Table I. In general, it will be observed that good to excellent results were obtained in almost all cases of seasonal rhinitis. While the dosage was adjusted as required, the majority of the patients received 4 mg t.i.d. When smaller dosages were prescribed (1.0 to 2 mg t.i.d.) it was sometimes necessary to increase the

*Chlor-Trimeton supplied by Schering Corporation, Bloomfield, New Jersey.

TREATMENT WITH CHLOR-TRIMETON—SEIDMON

dose before the desired relief was obtained. The rate of improvement in symptoms was variable, with some patients noting almost immediate relief while others required as long as thirty minutes for maximum effectiveness. When asthma was present, in conjunction with allergic rhinitis, a vasoconstriction of the nasal mucous membranes was noted with little or no improvement of the wheezing.

Two patients who had reported drowsiness with other antihistaminic agents experienced relief of symptoms and no drowsiness with Chlor-Trimeton. Two hay fever patients who had previously obtained relief with Tripeleminamine hydrochloride asked to be returned to the latter. One patient who had fair results with Trimeton reported faster relief with no side effects when Chlor-Trimeton was substituted.

Urticaria.—As has been observed with other antihistamines, all cases of urticaria responded well to Chlor-Trimeton therapy. Four experienced almost immediate relief and three cleared more slowly. In one case of giant urticaria, itching stopped in one to two hours, but edema did not subside for one week.

Bronchial Asthma.—Of seven cases of bronchial asthma treated with Chlor-Trimeton in this series, three reported excellent results, two good and two poor. It is generally agreed that the antihistaminic drugs are of little value in the treatment of wheezing. While this series of asthmatic cases is too small to draw any conclusions, the observations in this group are in keeping with results generally reported, namely, that children with bronchial asthma respond better to Chlor-Trimeton than do adults. Results in the treatment of asthma do not indicate it to be the drug of choice for this condition.

Nonseasonal Allergic Rhinitis.—Two cases with allergic rhinitis responded promptly with excellent results, one received some relief, and in two, sneezing and nasal discomfort were not alleviated.

Miscellaneous Allergic Conditions.—One case of dermatitis medicamentosa in a thirteen-month-old infant received 1 mg t.i.d. The itching stopped and drying up of the skin lesions resulted in three days. A case of ragweed dermatitis failed to respond to therapy, whereas a patient with dermatitis venenata reported relief of itching in a day. Pruritus from poison ivy dermatitis was relieved in one day. One case with cephalalgia also experienced rapid relief with the drug.

SIDE EFFECTS (TABLE II)

It was observed that side effects were of a mild nature, and in almost all instances medication did not need to be discontinued because of them. Of the 101 patients in this series, thirty-one or 30.1 per cent reported side

TREATMENT WITH CHLOR-TRIMETON—SEIDMON

effects. In one case only was the medication discontinued because of undesirable reactions. Two cases reported moderate or severe drowsiness, while the remainder reporting drowsiness did not complain of the slight sedation. None refused to continue the drug because of it.

TABLE II

Side Reactions		Number of Cases
Drowsiness	Slight	23
Drowsiness	Moderate or Severe	2
Headache	Slight	2
Vertigo	Slight	2
Urticaria	1
Diarrhea	Slight	1
Total		31

The nature and number of side effects observed in this series appear to parallel findings reported previously^{1,2,4,6} that the degree of side effects with Chlor-Trimeton was found to be less than observed with other antihistamines.

SUMMARY

Chlor-Trimeton in dosages from 1 mg t.i.d. to 4 mg t.i.d. was administered to 101 patients chosen from office and clinic patients. The age groups ranged from thirteen months to forty-eight years, with thirty-three patients being under fourteen years of age.

Patients studied complained of hay fever, asthma, urticaria, nonseasonal allergic rhinitis, and other allergic complaints. Sixty-one per cent reported excellent results and 32 per cent good results. Relief of symptoms with Chlor-Trimeton was not obtained in 9 per cent of the cases.

While side effects were observed in 30.1 per cent of the patients, these were of a mild nature in almost all instances.

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389

THE ROLE OF BACTERIAL ALLERGY IN THE RHEUMATOID STATE

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RHEUMATIC fever and infectious or rheumatoid arthritis are receiving increased attention from allergists as more is learned about the nature of bacterial sensitivity and its disease manifestations. As a result, the field of allergy may be greatly augmented. Rheumatic fever and arthritis alone affect 7,500,000 Americans, according to the Arthritis and Rheumatism Foundation. It is yet to be determined how many persons are afflicted by the other forms of bacterial allergy, such as certain types of chronic sinusitis and asthma. Nevertheless, sensitivity to bacteria and the various consequent symptomatic syndromes already have become of prime interest to both the general practitioner and the allergist.

This report presents a procedure that has been used for the diagnosis and treatment of rheumatic fever and infectious or rheumatoid arthritis, not as infections but as manifestations of allergy to bacteria. In essence the procedure resembles the usual one for allergy: i.e., the patient is tested for sensitivity to 150 to 200 strains of bacteria by the method of Blatt, Nantz and Rehm,^{1,2,3} and, if he reacts, he is treated by a program of desensitization. This form of diagnosis and treatment has been applied to 283 patients who presented the clinical symptoms of rheumatic fever or infectious arthritis. The protocols of representative cases are presented to illustrate the nature of the results obtained with the test and to indicate what may be expected with this type of therapy.

In doing the test, if most of the white cells show necrosis, the reaction is designated *completely necrotic*; otherwise when there is significant necrosis it is designated *seminecrotic*. In either case the test is *positive*, and the patient is considered to be sensitive to the filtrate eliciting the reaction.

An allergic patient is usually sensitive to four or five different filtrates. The filtrates to which he is sensitive constitute his *sensitivity pattern*.

The test is run on two samples of blood drawn on different days, and, if a positive reaction is obtained on the samples, a third sample is tested for additional confirmation.

In no case is a sensitivity pattern considered to have been established unless each of the filtrates in the pattern is confirmed by the clinical picture. In none of the 283 patients has any inconsistency between the sensitivity pattern and the medical history been encountered.

Incidental confirmation of the sensitivity pattern may be obtained during the program of desensitization when a step-up in the strength of the injection causes a reaction.

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BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

Final confirmation comes when the program of desensitization is completed and tests for each filtrate in the pattern become negative. It is axiomatic that all tests must be completely negative at the end of the desensitization program.

PROCEDURE FOR DESENSITIZATION

The same filtrates are used for the desensitization injections as were used in making the sensitivity tests. If the patient is sensitive to two or more filtrates, these are combined to make a *polyfiltrate*.

Before the first injection, the patient is skin tested with 0.05 cc of 1:1,000,000 dilution of his polyfiltrate. If he has no reaction, he is given subcutaneous injections, twice weekly, beginning with 0.05 cc of the 1:1,000,000 dilution. The dosage is stepped up by 0.05 cc each time. Whenever there is a reaction, the dosage is repeated in the next injections until it is well tolerated.

When the patient has taken and tolerated 1 cc of a 1:1,000,000 dilution he is given 0.05 cc of the 1:100,000 dilution, and so on. Some patients are able to progress to full strength filtrate; others get reactions every time they are given 1:10 or 1:100 or, in some cases, even 1,000 dilution. In such cases the patients are given injections of the maximum dosage they will tolerate, at the maximum interval (usually semimonthly or monthly) that will permit them to maintain tolerance and prevent the recurrence of symptoms. During seasons when the symptoms had previously been most acute, the interval may need to be shortened to maintain remission of symptoms.

When the patient is receiving the maximum dosage that he can tolerate, the sensitivity tests are repeated. They should all be negative.

PRECAUTIONS

The filtrates are kept refrigerated because heat destroys them. Sterility tests are run at regular intervals because no preservative can be used. Each patient is assigned a syringe which is not used on any other patient. Before use, each syringe is flushed in tap water, then sterilized in distilled water and in the autoclave to avoid pyrogens.

As is customary in the management of atopic allergies, desensitization is not initiated at the peak of a flare-up in order to avoid violent reactions.

CASE REPORTS

Rheumatic Fever

Case 1.—Rheumatic fever in the acute phase. The first case is an eleven-year-old girl who was examined the first day of her clinical attack of rheumatic fever. Her family background showed nothing pertinent except that her grandmother had had tuberculosis. The patient herself had had the ordinary childhood diseases: measles, mumps, chicken-pox, and whooping cough. During early childhood she had had frequent colds.

At the age of eight a suppurative otitis developed. This disappeared following a tonsillectomy and adenoidectomy. She had no subsequent complaints except frequent

BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

sore throats. Three months before the clinical attack of rheumatic fever, the suppurative otitis recurred. Five weeks before the attack, the entire family and she had had severe sore throats.

A week later irradiation to the nasopharynx was given, and the ear ceased running. Three days after the last treatment a pain developed in the fingers and migrated to the left elbow and wrist, causing external swelling and limitation of motion. The next morning the pain had wandered to both knees and down the left ankle. Her parents concluded that she must be having an x-ray reaction and called the doctor.

The inner aspect of the foot was erythematous, edematous, warm, and tender. There was a tachycardia of 120 beats per minute but no murmurs. The temperature was 99.4°. She was hospitalized.

On the following day the inner aspect of the left foot was slightly swollen, tender to touch, and erythematous. The heart was not enlarged; however, there was a sinus arrhythmia, and she now had a soft, grade one systolic murmur. Serology was negative. The tuberculin test was negative. The white count was 9,400. The corrected sedimentation rate was 41. Nose and throat cultures showed *hemolytic Streptococcus aureus*. An electrocardiogram revealed a right axis deviation. PR interval was 0.14. X-rays of the feet and ankles in frontal and lateral projections showed no abnormalities. In particular, there were none of the productive or destructive changes in the region of the foot or ankle which might have accounted for the clinical complaint of joint pain. The frontal and left lateral x-ray projections of the chest were normal.

The first sensitivity tests were run twenty-four hours after hospitalization. The second and third runs were made on the next two days. Each run consisted of tests to approximately 120 bacterial filtrates, including Lancefield's Group A *hemolytic Streptococci* Nos. 1 to 47. On each run the same three strains of Group A *hemolytic Streptococci* and one *Streptococcus viridans* were markedly positive.

Ten days later the program of desensitization to the positive-producing filtrates was begun. At this period we were still stepping up amount injected by 0.1 cc instead of 0.05 cc at a time. All swelling had subsided by this time, but a low-grade temperature and a tachycardia of 120 remained.

The first injection of 0.1 cc of 1:1,000,000 dilution produced a reaction six hours later. The temperature rose, the joints swelled and pained. The dosage had to be repeated four times before it was tolerated. The reaction recurred each time the dosage was stepped up 0.1 cc until 0.1 cc of 1:10,000 dilution was given.

Because of these reactions the desensitization program has taken much longer than usual, and she is now being given 1:1,000 dilution. She has been afebrile for nearly two years, with a normal cardiac rhythm and no murmur. She has had no joint symptoms or pain. The last sedimentation rate was 14. She now participates in all normal activities without restriction. In January, 1950, her blood was retested to the filtrates of her sensitivity pattern. The results were negative.

Similar case reports have been prepared for a thirty-four-year-old woman who was desensitized two months after her first clinical attack had subsided, and for a thirty-eight-year-old woman whose rheumatic fever was of the long-standing, recurrent type. These are not being printed in full because of lack of space. An additional case, representing a situation where sensitivity had set in but no symptoms were yet manifest, would have been highly desirable. As yet, however, such a case has not been encountered. All the children of parents who have had rheumatic fever have been tested. Those who have been found negative have been retested

BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

during and following each cold or other respiratory infection. So far none of these children have had rheumatic fever nor have they developed a positive test. Should some of them contract the disease and develop a positive test, it is hoped that more will be learned about the predictability of rheumatic fever and the onset of sensitivity.

During the program of desensitization, patients gradually lose their symptoms. Not uncommonly, they report feeling "completely well" before their tests become entirely negative. Apparently, if they then discontinue their program, their symptoms gradually begin to recur.

Rheumatoid Arthritis

The medical history and symptoms reported by patients who have had rheumatic fever are sometimes remarkably similar to those reported by patients having arthritis, especially those having infectious arthritis as distinguished from traumatic, hormonal, and other types of arthritis. In some cases, there is apparently little if any connection between the two diseases. In many arthritic patients the allergic base is easily overlooked because of certain symptoms.

Case 2.—Arthritis with infectious nature obscured. In the case of this thirty-three-year-old white male, the possibility of bacterial sensitivity was not immediately suspected because of a normal sedimentation rate and what seemed to be evidence of a protruding disc.

The patient had suffered from a low back pain for many years. He had received temporary relief about eight years prior to the present studies from twenty-seven chiropractic treatments. The patient had suffered from repeated colds for many years. For the past two years he had had a pain in the left buttock which worsened in damp weather and which lately had radiated down the left leg. Coughing aggravated the pain markedly. For a time there had been numbness of the toes, but this had disappeared. He did not notice any weakness of the leg muscles.

Examination of the back revealed loss of the usual lumbar lordosis and slight left convex scoliosis in this segment of the spine. There was marked spasm of the paralumbar muscles, and forward bending was limited to 20 per cent of normal. No tenderness could be elicited over the spine, but it was marked over the left gluteal musculature, especially at the sciatic notch. Tenderness was also present along the course of the sciatic nerve on the left side as far down as the knee. Raising the left leg in a straightened position produced pain at 140 degrees, and the Lasegue's sign was positive. The reflexes, motor and sensory, were normal; the feet showed tenderness in the plantar fascia but were otherwise normal.

X-ray examinations of the lumbar spine and pelvis revealed some lipping of the bodies of the vertebrae, especially on the fourth lumbar. There was a loss of lordosis. The lumbosacral apophyses were in different planes. There was some moth-eaten tendency about the sacroiliac joints.

The corrected sedimentation rate was 3; serology, negative. The urine, chemically and microscopically, was negative. The blood count and hemoglobin were normal; the white count, however, was 11,250 with a normal differential.

The apparent diagnosis was severe acute left sciatica due, perhaps, to a protruded disc at lumbar 5, and possible arthritis of the sacroiliac joint.

When a back brace, shoe corrections, and paraffin packs produced no improvement in three months, sensitivity tests were run. He was tested to all the bacterial filtrates

BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

in our collection and was found positive, on each of the three runs, to a pattern of four different Group A hemolytic *Streptococci* strains.

In the desensitization program, five hours after receiving the 0.4 cc of 1:1,000,000, he had a marked general reaction: temperature, chills, and pain. This recurred in the same manner each time the dose was increased 0.1 cc until he was taking 0.25 of the 1:100,000 dilution.

For the past two years he has been free of pain and other symptoms; he can bend freely and do heavy lifting. His sensitivity tests are now negative. He is maintained on bimonthly injections of full-strength filtrate, as a control on other negative patients who tolerate full strength filtrate but whose doses have been entirely discontinued.

Case 3.—Typical arthritis of infectious nature. The last case is one typical of many where nonspecific inoculations (typhoid here) do not desensitize though they may relieve temporarily. In 1946 a fifty-year-old woman came complaining of swelling, stiffness, and severe pain in most joints. Her condition was worse in damp weather.

The first symptom to develop had been the swelling and stiffness of the knees. The pains in the back and shoulder joints and swollen feet developed gradually. Extreme fatigue and shortness of breath had been recent concomitants. There had been no loss of weight, no chronic low-grade temperature, no evidence of past rheumatic fever or other previous joint disease. In childhood she had had scarlet fever but, evidently, without sequelae.

On examination, the temperature was normal. The blood pressure was 110/70. The corrected sedimentation rate was plus 50. The Kahn test was negative. The urinalysis, blood count, and electrocardiogram, taken with multiple chest leads, were all within normal limits.

Chest x-rays showed no pathology except that the heart was slightly enlarged.

X-rays of the paranasal sinuses showed an opacity in the right maxillary sinus in the external lateral wall of the sinus, suggestive of mucosal thickening rather than empyema. Roentgenograms of the knees and shoulders showed no bone pathology.

Her condition became steadily worse, until she could no longer dress herself, despite the usual therapies of high vitamin diets, paraffin packs, colloidal sulphur, bee venom, and lastly typhoid. Finally, her fingers became swollen and she could no longer bend her knees. Only the typhoid fever therapy had any effect, i.e., for a time she was able to dress herself. The shortness of breath, swellings, and severe pains, aggravated especially in damp weather, continued.

In May, 1948, the patient became interested in the research in progress and asked if she might not be tested. Marked positives were obtained to the filtrates of two Group A hemolytic *Streptococci* strains and one *Staphylococcus aureus* strain.

The program of desensitization was begun with 0.05 cc of the 1:1,000,000 dilution of the positive-producing filtrates. Several hours following the inoculation with 0.4 cc a general reaction occurred, with temperature and joint pains. The same phenomenon occurred with 0.4 cc of the 1:100,000 and 0.4 cc of the 1:10,000 dilutions. It occurred again when she received 0.3 cc of the 1:10 dilution.

She has now been free of pain in all weather for more than two years. She has normal motility of all joints and no swelling. Her sensitivity tests are negative but, again as a control case, she is being maintained on bimonthly injections of the full-strength filtrate.

DISCUSSION

Ordinarily the desensitization program results in one or more interim reactions: in the gradual but complete remission of symptoms and, even-

BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

tually, in negative tests to all filtrates in the sensitivity pattern. These results are the same regardless of the amount of necrosis in the initial tests.

Among the 283 patients, there have been a few cases unresponsive to treatment, only three of which could not readily be accounted for by some extraneous factor such as unavoidable variation in the procedure. These three patients were all middle-aged and had had arthritis for more than fifteen years. Their medical histories and clinical findings presented clear-cut pictures of infectious arthritis which in no way were unusual or deficient. These three patients were subjected to the usual program of desensitization and eventually were able to tolerate full-strength injections of the polyfiltrates prepared for them. Yet none showed any clinical improvement; none had even a single reaction throughout the desensitization program and, on retesting, each one was still sensitive to all the filtrates in his sensitivity pattern.

As yet, no satisfactory explanation has been found for these three failures. The only apparent clue is the fact that all the positive tests in each of these cases, both before and after desensitization, were of the seminecrotic type. Among the possible explanations that have been considered are the following:

1. Variation in the potency of the filtrates. Strong filtrates could cause complete necrosis, weaker filtrates only seminecrosis. This was ruled out by the fact that the same filtrate caused complete necrosis of one patient's leukocytes but only seminecrosis of another's.

2. It could be that in the sensitivity pattern of several filtrates, one is the *basic sensitivity* while the others are only supplementary. The 3 per cent who were found sensitive to but one filtrate had, then, *no supplementary sensitivities*. Accordingly, they could respond to desensitization to one filtrate both as regards their symptoms and their tests.

The 97 per cent who were sensitive to more than one filtrate responded because the sensitivity patterns to which they were desensitized included their *basic filtrates*. The three who failed to respond did so because desensitization was attempted with only their supplementary filtrates. It being impossible to desensitize without the basic filtrate, they retained their symptoms and their tests remained positive.

This explanation has not been completely ruled out. The collection of bacteria available for the tests does not yet contain every bacterium pathogenic to man. It would be possible, therefore, if there is such a thing as basic sensitivity, to discover the supplementary sensitivities but fail to find the basic one. The practice of frequently not testing for the filtrates of the rare bacteria in the collection furthers this possibility.

3. It was suggested that the filtrate might contain several components of varying power to produce necrosis. Then, if a patient were sensitive to a component which was powerful, his leukocytes would become completely necrotic. If, on the other hand, he were sensitive to a component

BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

which was weak, his white cells would become only seminecrotic. However, this possibility was ruled out by the histories kept for the individual filtrates; these list the reactions each has caused. Every filtrate which had caused seminecrosis for one of the three failures had caused seminecrosis for several middle-aged, long-standing arthritic patients who responded normally. Desensitization seems equally effective for all degrees of necrosis.

4. It was suggested that seminecrosis could be caused by the patient's being allergic to a certain one of the several chemical components of a filtrate, which chemical, in varying quantities perhaps, is present in each of the filtrates of his sensitivity pattern. This would mean that, when much of this chemical is in a filtrate, there is complete necrosis; but when there is comparatively little of it, there is seminecrosis. This is not likely, because an occasional patient can have lost his symptoms, and be taking injections of 1:1,000 or even 1:100; yet, when he is retested, he may continue to be sensitive to one of the filtrates of his pattern, but have lost his sensitivity to all the others.

5. It was suggested that there might be a synergistic factor in the filtrate pattern. This was ruled out by the 3 per cent who were sensitive to only one strain, because they responded as well to desensitization as did those with polyfiltrate patterns. Furthermore, the filtrates in these one-filtrate patterns were each also included in the polyfiltrate patterns of other patients.

6. It was suggested that the amount of necrosis might be a characteristic of a disease, but the records definitely show no such fact.

7. It was suggested that arthritic damage, by its very nature, at some point becomes irreversible, and that seminecrosis is somehow associated with the mechanism of this irreversible damage. This, however, is not consistent with the fact that arthritic patients, who were older, had suffered more acutely, had had arthritis longer, and likewise had had seminecrotic tests throughout, responded in the usual manner, i.e., got reactions during treatment, and, when dosage had reached dilutions of 1:100 or 1:1,000, lost all symptoms and gave negative tests. This, however, actually neither proves nor disproves the existence of a secondary form or stage of sensitivity; neither does it explain seminecrosis.

Since no explanation so far investigated has been found valid, new lines of inquiry will be necessary to account for the failures. Accordingly, additional types of records are now being kept to make analysis of other facts possible.

CONCLUSIONS

1. Rheumatic fever and infectious arthritis are diseases caused by bacterial allergies. In proof, (a) the blood leukocytes of patients exhibiting the clinical manifestations of these diseases become necrotic in less than eighteen hours in the presence of certain, but not all, bacterial filtrates; (b) overdosage during the desensitization program produces reac-

BACTERIAL ALLERGY IN RHEUMATOID STATE—BLATT

tions reproducing the syndromes of the diseases; (c) injections of filtrates to which a patient is not sensitive, or of saline solution, produce no reactions; (d) the patient's symptoms disappear following injections of the filtrates to which they were found sensitive; (e) after a program of desensitization, the patient's leukocytes are no longer sensitive to the original bacterial filtrates.

2. Although all rheumatic fever and rheumatoid arthritis patients were sensitive to one or more Group A *hemolytic Streptococci*, there was no characteristic sensitivity pattern found for either disease.

3. The amount of necrosis may vary (a) for the same filtrate between two patients having the same disease and the same symptoms, (b) for the same patient between two different filtrates in his sensitivity pattern.

4. A program of desensitization to the bacterial filtrates to which the individual is sensitive results in the gradual diminution of symptoms, generally one or more interim reactions, and, eventually, in the loss of all symptoms and sensitivities. These facts evidently are not affected by (a) the age, sex or race of the patient, (b) the duration, phase or associated symptoms caused by the disease, (c) the composition of the sensitivity pattern, or (d) the degree of necrosis.

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580 *Doctors Building*

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(Continued from Page 359)

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397

The Editor's Page

INCIDENTAL to a discussion on the essence of physiological rhythmic changes, Mentzel¹ mentions that vital capacity studies show that in asthmatic patients, and in those with thyrotoxicosis, there is a hyperkymatic daily curve. At night, the vital capacity falls 27 to 58 per cent of the day's highest level. A cursory examination of the American literature finds no mention of this important observation. Confirmation would make an interesting short paper for some future issue of *ANNALS OF ALLERGY*.

In the experience of many allergists, typical migraine is rarely found to be truly allergic, although food sensitivity does often present itself in headaches occasionally migrainoid in character. There is, as yet, an unexplored field in this regard, despite the many published papers as shown by a recent communication by Wit,⁴ who studied seventy women with migraine. Of these, there were thirty-eight in all of whom the symptoms were both premenstrual and menstrual and associated with positive tests to Dimenformin (Estradiol 3-benzoate). In eleven, the local reaction caused an attack of migraine. In twenty-eight, in whom there were no allergic reactions to estrogens, there was no relation between the menses and the onset of the headaches. Fellows of the College who would like to pool their research resources in this regard may communicate with each other by means of the Office of the Managing Editor. The Editors will be particularly receptive to any paper which helps solve the problem of the relationship between migraine and allergy.

Tabart² brings forward a new treatment of migraine, using aerosol procaine (1 per cent) in diffuse and premenstrual migraine and ergotamine aerosols in paroxysmal, isolated or prolonged attacks. The patients, fourteen in the first group and nine in the second, had resisted all other forms of treatment. In thirteen patients both aerosols alone or combined failed to relieve symptoms. There were signs of intolerance in only one individual. If these results are confirmed, it would appear that we have one other means of treating a distressing, often recalcitrant, condition.

It may be possible that in patients with bronchial asthma, ephedrine is not being used in sufficiently large doses. According to Whitfield et al³ doses of 1 gr in all of eight asthmatic patients produced an increase in vital capacity and in complemental and reserve air with subjective relief and clinically observed decrease in dyspnea. In one additional patient, the dose was 2½ gr. Doses of ½ to 4 gr had no such effect in emphysematous nonasthmatic individuals or in normal controls. Although doses of 1 gr or more produced headaches, faintness, nausea, palpitations, the use

(Continued on Page 416)

Progress in Allergy

DERMATOLOGIC ALLERGY

A Critical Review of the Literature in 1950 on Allergic Eczematous Dermatitis, Atopic Dermatitis, Drug Eruptions, Urticaria

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A SURVEY of the literature dealing with dermatologic allergy which appeared between the latter part of 1949 and through 1950 leaves the impression that some shift is occurring in interests and approaches to problems in allergy. It is to be expected, and it is reasonable, that new concepts and new therapeutic agents should attract eager work and enthusiastic report, in part at the expense of older concepts and well tried therapeutic agents. Thus while there has been a solid block of papers on the usual topics, we detect in the American literature the beginning of a recession with regard to the anti-allergic effects of the antihistamines and the allergenic effects of antibiotics. Psychosomatic interpretations are less in evidence. In place of these there is appearing a flood of articles concerning the effects of adrenocorticotrophic hormone and cortisone on allergic states. The reports dealing with these hormones are still too preliminary and fragmentary for critical review, and it will be another year or two before evaluation is likely to be profitable. Segal and Herschfus⁶¹ in their review in *ANNALS OF ALLERGY* have listed some of the pertinent references. However, readers may be interested in a very short summary of what is the authors' present opinion of the indications for ACTH and cortisone therapy in allergic dermatoses and of their effects on cutaneous reactions. These opinions are a composite of the authors' own experiences and the evidence available in the literature.

SHORT SUMMARY OF EFFECTS OF ACTH AND CORTISONE IN ALLERGIC CUTANEOUS ERUPTIONS AND REACTIONS

Just as in certain other allergic diseases such as bronchial asthma and allergic rhinitis, ACTH and cortisone *do not produce cures* in any of the "major" allergic dermatoses, i.e., in allergic eczematous dermatitis, atopic dermatitis, urticaria and angioneurotic edema, and allergic drug eruptions. However, these hormonal agents while they are being administered exert dramatic effects in some cases of allergic dermatoses. There is usually a return of symptoms and signs of the disease within a more or less short period of time after cessation of therapy unless (1) the allergic reaction has run its full course during the period while the patient was under treatment or (2) it has been possible to find and/or eliminate the allergenic agent, or agents during the period while the patient was under treatment.

In allergic eczematous contact-type dermatitis there is an effect from ACTH and cortisone on the inflammatory part of the reaction, on the associated itching, and apparently even on the characteristic vesicular part of the eruption. However, experience in this type of eruption is, as yet, very limited. ACTH and cortisone are not indicated in allergic eczematous contact-type dermatitis, unless they are administered with the specific purpose in mind of giving the patient some symptomatic

PROGRESS IN ALLERGY

relief while he is going through the very severe pruritic and inflammatory phases of his eruption.

In atopic dermatitis the effect of ACTH and cortisone is usually very striking. Within a few hours after administration of the hormone, itching becomes less severe or subsides, and within a few days an eruption which may have been present for many weeks, months or years gradually undergoes partial or complete involution. It has been one of the authors' more remarkable clinical experiences to observe resolution within a few days of patches of thickened and lichenified skin which have been in existence for a long period of time and which look as though they must take months to resolve. Nevertheless, at present the indications for the clinical use of ACTH and cortisone in atopic dermatitis are as follows: (1) To control severe acute exacerbations of an otherwise relatively stationary or torpid eruption. In such cases the "acute" process probably is often self-limited and the hormonal agents merely suppress an important part of the inflammatory response and the itching. It is useful then to tide over a patient in an episode of exacerbation that is going to be of short duration. (2) To permit orthodox forms of therapy, such as proper topical therapy, antihistamines by mouth (a sign of the recent developments in the management of allergic dermatoses that antihistamines now are included among the "orthodox" medications!!), et cetera, to once more become effective. This refers to those *severe* cases of atopic dermatitis in which the patient cannot obtain relief from any of the accepted forms of therapy, i.e., where he is in a state which is in some ways quite similar to status asthmaticus. When ACTH or cortisone is administered in such cases, even if these agents do not completely control the eruption and the itching, some patients again respond to topical medication and systemic antipruritic therapy. (3) While ACTH and cortisone should *not* as a rule be used in atopic dermatitis over a long period of time, there are some otherwise intractable cases in which very small maintenance doses (e.g., cortisone 25 mg daily) are adequate to keep away the eruption and itching. In such exceptional cases it seems warranted to continue the hormonal medication over protracted periods of time.

In urticaria and angioneurotic edema ACTH and cortisone in many cases have a partial or complete suppressive effect on the lesions while the agents are being given, but we have yet to see a case of *chronic* urticaria or angioneurotic edema in which these agents have a curative effect. Thus here again ACTH or cortisone can be used to ameliorate symptomatically a particularly severe or persistent eruption, but in principle these agents in urticaria should not be considered any more of a "cure" than an epinephrine injection.

As far as the classical allergic and nonallergic cutaneous responses to *skin tests* are concerned, the literature and the tests performed by our own group⁶⁰ to date indicate the following activities of systemically administered ACTH and cortisone:

- Allergic urticarial reaction: no significant effect
- Nonallergic urticarial reaction: no significant effect
- Allergic eczematous reaction: no significant effect
- Nonallergic eczematous reaction: no significant effect
- Allergic tuberculin-type reaction: quantitative reduction, but apparently not complete abolition, in some cases.

All these tentative statements regarding the effects of ACTH and cortisone refer to the use for seven to ten days of those dosages of the hormones which, at this time, are accepted for routine therapy. It appears quite possible that with larger doses and/or with more protracted periods of administration much more regular and intense, perhaps even different effects could be achieved in some clinical eruptions and that other changes in the skin test responses might be brought about.

PROGRESS IN ALLERGY

ALLERGIC ECZEMATOUS DERMATITIS

Two papers have appeared on the specific management of poison ivy dermatitis with materials that are somewhat different from those which had previously been in common use. Gaillard,¹⁹ with a prophylactic purpose, administered subcutaneously an aqueous alum-precipitated pyridine extract of poison ivy to 100 subjects who were known to be sensitive to poison ivy. This preparation was developed several years ago by Strauss and Spain.⁶⁷ Preseasonal treatment was carried out over a period of three years, and the percentages of cases in which benefit is claimed are 77 per cent for the first year, 84 per cent for the second, and over 90 per cent for the third year. The extract was not administered during acute episodes of poison ivy dermatitis, and thus no judgment is made of possible effectiveness of therapy in established poison ivy dermatitis. However, Keil³⁵ used 3-n-pentadecyl catechol in a group of some forty patients in various stages of acute dermatitis from poison ivy, and he observed considerable shortening of the course of the eruption both symptomatically and objectively. This simple chemical is either one of the active principles of poison ivy or is immunochemically so closely related to one or more of the active principles of this plant that it produces positive patch tests in almost 100 per cent of the patients who have an allergic eczematous contact-type sensitivity to poison ivy.

The studies both of Gaillard and of Keil deserve and require repetition by other investigators. While the exceedingly promising results as reported are properly qualified with reservations, there are certain problems in the evaluation of results of prophylactic and active treatment routines in conditions like poison ivy dermatitis that demand very special consideration and checking by many investigators. For example, the over-all control of a group large enough to be statistically valid to test such routines is exceedingly difficult. In the case of exposure to an external factor like poison ivy, degree of contact depends among other factors on botanical conditions that promote or curtail the lushness of plant growth, on changing habits of the group, on weather conditions that influence the wearing of clothing which may offer protection, and many other uncontrollable factors. Even the very fact of preseasonal treatment introduces an awareness and a newly acquired knowledge of the danger of exposure that may influence equality of conditions before and after inception of the treatment. Neither Gaillard nor Keil ran a control group that received "placebo" treatment and that could have been compared with the group treated with specific extract or simple chemical. However, Hoagland,²⁸ working with *older types of poison ivy extracts*, but with a controlled military population, and taking into consideration the variables that still obtain, found no benefit from prophylactic injections. Comparative evaluation of different treatment schedules is equally fraught with statistical and other difficulties. For one thing, it is well known that cases of poison ivy dermatitis vary within wide limits of mildness and severity. Factors of secondary infection, location of the eruption (worse on hands and feet), and concurrent topical treatment (if only protective dressings) all enter into final consideration.

It is well to realize that aside from all the uncertainty as to the extent to which prophylactic and particularly active treatment with poison ivy extracts or related allergens are efficacious, the whole theory of these procedures still rests on insecure grounds. Knowing as little as we do of the interaction of skin-sensitizing antibody with the antigen, and knowing nothing at all about neutralizing antibodies in the eczematous type of sensitization, it is hard to theorize as to what happens when one administers an allergen within an established although quiescent allergic state and even harder as to what may be expected from administration within an acute episode of allergic response. Particularly in the latter instance, where most of the damage has already been done by the time the patient consults the physician, it appears most reasonable to direct treatment to the morbid morphologic change; and it is difficult to imagine what good the administration of the noxa could do in such a situation.

PROGRESS IN ALLERGY

The problem of allergic eczematous dermatitis from cosmetics and "beautifying" routines becomes knottier as the number and variety of agents used and the number of persons using them increases, and finally as the number of applications of various substances per unit of time becomes augmented. Whitacre and Parsil⁸⁵ list ingredients that are very commonly used in the production of cosmetics and cite authorities that have found them to be either primary irritants or sensitizers. They also discuss the manufacturer's responsibilities regarding undesirable skin reactions entailed in connection with the production of cosmetics. Rein and Rogin⁸⁶ carefully worked up forty-seven cases of nail bed changes which followed use of nail "under coats." By patch testing with several separate agents that are contained in this cosmetic auxiliary, they confirmed the basic allergic eczematous nature of these nail changes which had been suggested by Sulzberger et al.⁷³ What is more startling, they offer proof that the allergenic material in the solvents contained in the nail "under coats" actually penetrated the nail plate to reach the reaction site. This finding opens the way for future work where nonallergic diseases of the nail bed such as psoriasis and fungous infections may be treated with topical medicaments which could penetrate the nail plate.

Furman, Fisher and Leider¹⁸ report another, apparently hitherto unrecognized, source of allergic eczematous contact dermatitis from rubber sponges used for the application of cosmetics. Within a period of three years they observed twenty-six cases of dermatitis of the face proved by patch test to be caused by such rubber sponges. Aside from recording another instance of an odd agent to produce trouble, this work points up a detectable cause for a clinical picture which in the past has at times been confused with seborrheic dermatitis, atopic dermatitis, contact dermatitis of other causation, and other dermatoses.

For some time now it has been known that allergic states, even when the primary causative allergen has been discovered and eliminated, often can become clinically evident by the action of immunochemically related secondary allergens to which cross-sensitization or group sensitization exists. Perhaps the most common example is the group of substances which includes certain sulfonamides, local anesthetics, paraphenylenediamine, azodyes, and numerous chemically related substances.⁴ Baer and Leider,³ pursuing this phenomenon, fed azodyes, which in the United States are certified for dyeing foods, drugs and cosmetics, to patients who were sensitive to paraphenylenediamine and found exacerbations of symptoms or signs that suggested that the cross-sensitization may indeed extend to these food dyes, a phenomenon which on the basis of ingestion or other occult contact with these secondary allergens could explain persistence, exacerbation, or chronicity of some cases of eczematous dermatitis.

There are a number of other papers describing dermatitis due to azodyes which have been certified by the U. S. government. While in some instances these dyes themselves may be the primary and sensitizing allergens, in other, more frequent, instances they may be merely secondary allergens which elicit an allergic response in tissues which previously had become sensitized by an immunochemical relative with a higher sensitizing potential. Jaffe³² reports an example of an eczematous sensitization to such a certified dye that is used to color a particular make of commercially prepared oleoresins for patch testing. This event, of course, made interpretation of the patch test results impossible, because all the oleoresin materials sold by this particular supplier contained the same dye and thus all the test materials elicited positive reactions. Several similar cases which will be published by A. A. Fisher were seen at the Skin and Cancer Unit of the New York University Hospital. Here the causal dye was found to be F. D. & C. yellow No. 3. The reports by Anderson¹ of dermatitis from nylon hair nets and of Goldsmith²² of dermatitis from F. D. & C. orange No. 1 in a candy factory are other instances of sensitization to dyes of this type.

PROGRESS IN ALLERGY

Peck⁴⁹ observed multiple sensitization to antihistamines. After examining the chemical constitution of several popular antihistamines, he came to the conclusion that there is a sufficiently close chemical relationship between certain of these compounds to account for a crossing over of allergic sensitivity to several others from primary sensitization to one of them.

The question of specific sensitivity to ingested foods as a factor in various types of eczematous dermatitis (i.e., of papulovesicular eruptions—not atopic dermatitis) has long been argued by students of dermatology and allergy, and is still unsettled. Livingood and Pillsbury³⁹ in an extensive paper make out a strong case for foods as a cause in some patients with recurrent vesicular dermatitis of the hands and with eczematous eruptions in other locations. That some cases are allergic eczematous contact-type dermatitis due to simple chemicals and other contact allergens, that some are dermatophytids secondary to fungal foci of infection elsewhere, that some are nummular eczema of unknown cause, and finally that others are psoriasis, pyodermas, bacterids, dyshidrotic eczemas, et cetera, are all well known facts. But after subtraction of all such cases that can be traced to acceptable causes or fitted into disease pictures of clear morphe, there remains a large group of cases where no clear decision can be made as to cause or classification. It is in this group that some believe sensitivity to foods is the mechanism and ingestion of specific foods is the basis of clinical episodes. Livingood and Pillsbury, following and extending the work of Rowe, Flood and Perry, Winston and Sutton and others, are modern proponents of this view and base their contentions on a series of carefully observed cases under trial of elimination and re-exposure to foods. Now, the principle of proof of allergic cause by elimination accompanied by clinical improvement and deliberate re-exposure resulting in swift clinical exacerbation can be very cogent in instances where the allergen is not a common one and where exposure to it is not complicated by occult exposure or cross-sensitization phenomena. In the case of foods as suspected causes of eczematous clinical pictures, we submit that elimination and re-exposure routines are not always very convincing. For one thing there is an unspoken implication that it is the characteristic protein of suspected foods that is the cause. But modern foods contain substances (simple chemicals) of less chemical complexity than protein which are nevertheless immunologically very active. The interesting papers by Livingood and Pillsbury and by Flood and Perry,^{16,17} although they contain statements that secondary infection and multiple causation play important roles, perhaps do not adequately consider the possible sources of error from elimination and re-exposure procedures. Nevertheless it must be said that the argument in favor of eczematous eruptions caused by ingested foods is becoming increasingly convincing.

Another topic that is always cropping up in the recent literature is the concept of autosensitization. Aside from its value in explaining some phenomena of the allergy of infection, it is applicable to some phases of eczema. A completely satisfying explanation of the wide dissemination of an eczematous process of allergic contact type has long been sought. To date there is no unanimity about the mechanism of the common clinical event of "the jumping of eczema." The most obvious explanation is that some allergens (e.g., plant allergens and topically applied eczematogenic drugs) are very easily widely and oddly spread by hands and contaminated clothing, manipulation of household objects, et cetera. A more subtle explanation employs the autosensitization theory. Cormia and Esplin¹² review Whitfield's concept and modifications of it by others. They then offer clinical observations and experimental findings which in their opinion prove that sensitizations to body-own substances occur. Such autochthonous products are said to arise at the site of an original dermatitis and provoke the formation of antibodies. Clinical eczematous pictures may then occur at distant points through interactions of antigen and anti-

PROGRESS IN ALLERGY

body, both of which have been transferred through the blood or lymph circulation. Unfortunately the experiments offered to prove the existence of autosensitization consist of demonstration of urticarial or tuberculin-type reactions rather than eczematous responses which one must demand as proof of eczematous autosensitization. We find this theory and its experimental support to date much less persuasive than the possibilities of physical transport of allergens on the surface, the creeping of allergens based on their individual characteristics of solubility in sweat, sebum, et cetera, and the capacity of some to penetrate seemingly impenetrable barriers (cf. Rein and Rogin⁵⁶ on penetration of allergens in nail "undercoats" through the nail plate). However, it is hoped that the interesting investigations on autosensitization to skin will be continued to some definitive decision.

White and Baer⁵⁶ were unsuccessful in lessening susceptibility of human beings to eczematous sensitization to dinitrochlorobenzene by applying to their skin sub-sensitizing doses of this chemical for several weeks prior to a potentially sensitizing exposure. In the course of this experiment they noted that a considerable number of subjects developed the "spontaneous" flareup phenomenon but several weeks later could no longer be shown to be hypersensitive to the chemical. They call attention to the potential clinical significance of this phenomenon, particularly in medico-legal cases.

Nexmand⁴⁷ has extended his previous work on cytologic differences between blister fluid from primary irritant and allergic eczematous reactions. He demonstrated that these differences hold true even when the two types of blisters are produced by the same materials in the same subject. Thus a primary irritant blister due to nitrogen mustard contained predominantly polymorphonuclear leukocytes, while an allergic eczematous blister due to nitrogen mustard contained predominantly lymphocytes and other mononuclear cells. Upon histological examination this same tendency was noted in the perivascular cellular infiltrate in the cutis. Nilzen⁴⁸ reported an inhibitory action of antihistamines on patch test reactions by adding the antihistamine to the test solution. This interesting experimental finding is not paralleled by any direct effect of antihistamine when topically applied to *clinical* eczematous lesions. Hellerstrom and Lundén²⁸ concluded from their tests that dermatitis due to turpentine is probably due to its oxidation products. Thus it appears likely that the freshly distilled batch of turpentine in general will be much less allergenic than the older batches which have had a chance to undergo oxidation.

Rithey⁵⁷ describes an excellent therapeutic result with BAL (dimercaptopropanol) in exfoliative dermatitis due to antimony. Jenkins³³ saw cutaneous sensitization to BAL both spontaneously after use of a BAL ointment in the treatment of thermal burns and deliberately produced in human subjects. With this he confirmed the previous work by Sulzberger, Baer and Kanof.⁷⁰

Gaul and Underwood²⁰ have published articles on the primary irritant and allergenic properties of the many substances that enter into the fabrication of footwear, particularly shoes. Their painstaking dissection of shoes, analysis and testing of cloths, leathers, gums, dyes, and tanning agents point up what those of us who have tried to ascertain allergenic causes in some of our patients' footwear have known for many years, namely, how many things that go into the making of shoes may go into the unmaking of feet. The situation also demonstrates the difficulty the physician has when a dermatitis of the feet has been traced to shoes—of advising and recommending other footwear. Some materials, like certain gums, are so common to most shoes that if such agents are at fault one could be tempted to advise futilely that the patient must resign himself to barefoot locomotion.

The popular slogan of "better living through chemistry" contains obvious truth but must be qualified. Some of the uses of chemical wonders are profitable for the manufacturer and seller but are obviously useless to the consumer, as in needless multiplication of cosmetics (how many colors and coats does one need to obscure the beauty

PROGRESS IN ALLERGY

of nature?), and some have a potential harm within a sphere of desirability. The increasing introduction of new chemicals that get on and in the body and the increasing realization of sensitizing possibilities have led to the study of how these and other undesirable qualities may be detected before wide use and resultant bad effects reveal dangerous qualities. One method advocated is the very much mislabeled "prophetic" patch test. The principle involved in this test is the establishment of the "sensitizing index," a term which was suggested by Sulzberger and Simon.⁶⁹ Holland and associates²⁹ discuss their experience with pre-patch testing as a means of determining the usability of agents that come into contact with the skin. They indicate awareness of many sources of error and many variables that enter into interpretation of procedures of this type. An impression is left that "prophetic" patch testing cannot be made a quick, simple, definitive, pre-judging routine. This is in agreement with our own experience which indicates that the "prophetic" patch test can be very unprophetic and should not be designated in a manner that makes it sound more useful than it really is.

Usage tests are ultimate and final determinants of a product's usability. Despite this situation there are certain practical advantages in uncomplicated standard pre-patch testing. So long as the statistical sample is large and general enough to be valid, the procedure is often capable of demonstrating *non-usability* of substances with a primary irritant potential and a high sensitizing potential. It must be realized that the patch test is not a method which has been adequately standardized for assaying primary irritants. Nevertheless it appears likely that a new substance that is inherently and inevitably a *primary* irritant will be quickly recognized as such. Also where *allergic* sensitization occurs in a high percentage of those exposed, say about 25 to 75 per cent, this will become obvious from these tests. The insufficiency of this testing method becomes obvious in instances of materials that are not *strong* primary irritants and where the irritancy can be modified to harmlessness or harmfulness by the many other existing factors such as local and climatic heat, friction, sweating, movement of materials on skin, et cetera. And if the sensitizing index of a substance is relatively low, the patch test on a sample of about 200 subjects often is incapable of revealing the seriousness of the situation because the sample of potential users that can be tested is usually inadequate and because such tests cannot simulate the natural circumstances where contact may be constant, frequent, and attended by variables which alone may be enough to convert a low incidence rate into a high prevalence rate. However, within these narrow limits there is a small place for this form of the patch testing.

Every year there are many reports of new substances and chemical compounds that are discovered to be causes of allergic eczematous contact-type dermatitis. Such reports are both educational and constant reminders that everything that approaches the skin should be suspect of being capable of sensitizing it and provoking clinical episodes. Following are representative examples:

Leider and Schwartzfeld³⁷ and Howell and Blair³¹ report five cases between them of allergic eczematous dermatitis from cocobolo wood. Four cases were from wood-handled objects with the eruption being on the hands, and one was from a musical instrument, resulting in a cheilitis. Since cocobolo wood is also used in fabrication of many other small wooden objects like trinkets, eruptions in other sites like wrists (bracelets) and the neck (necklaces) may occur.

Hollander³⁰ reports a new case of proven sensitization and eruption due to DDT. It is remarked that eruption of this cause is fortunately rare; otherwise this valuable agent might be more dangerous to human beings through sensitization than it is to lower forms of life through toxicity. The eruption has the characteristic distribution produced by an airborne allergen (exposed skin and such covered skin as receives the allergen by the chimney effect of clothes).

PROGRESS IN ALLERGY

Combes and Groopman¹¹ report two cases of contact dermatitis from thiamine, proved by patch test. The condition occurred in individuals who worked in a pharmaceutical establishment filling ampules with injectable materials.

M. Straus⁶⁶ reports two cases of eczematous sensitization to polyethylene glycols (carbowaxes). These substances are now widely used in vehicles for topical application, and as is a common experience with substances of relatively low sensitizing potential, no clear cases of sensitization had been reported previously. It can be expected that more such cases will be uncovered in the future.

This is a good place to dwell for a moment on the general matter of incidence and prevalence rates of eczematous sensitization. Incidence rate is the constant amount that arises out of the welter of factors that determine sensitization: namely, the inherent sensitizing capacity of the agent, number and frequency of exposures, and conditions of exposure (heat, sweating, oiliness, integrity of the skin, et cetera). Prevalence rate is what saves us from incidence. In chronic conditions it tends to be greater than incidence. For example, if a new substance has an incidence rate of sensitization of 1 per cent, at the end of one year the prevalence rate of established sensitization is also 1 per cent, but in every subsequent year it rises to 2, 3, 4 per cent, et cetera. To give another example of the numerical difference between incidence rate and prevalence rate, consider the number of women (and men) who cannot use nail polish because of sensitization. Since sensitization of this sort persists indefinitely, there are always a greater number of already sensitized persons (prevalence) than new sensitizations occurring (incidence) because prevalence is a sum of incidences.

Steiner and Leifer⁶⁵ saw three cases of dermatitis that were traced to tincture of benzoin. They were able to induce sensitization in two experimental subjects, and from the fact that these subjects had atopic dermatitis in one case and dermatophytosis in another they warn that care should be exercised in the use of tincture of benzoin on "persons with allergic diseases or a history of allergy." One cannot quite agree with this interpretation, for while it is well known that eczematous sensitization is promoted by pre-existing cutaneous damage, it is also known that no hereditary factor is necessary for this type of sensitization.

Describing two cases of an erythematobullous dermatitis clearly due to contact with iodo-acetic acids, Marcus and Frerichs⁴⁰ recognize the primary irritant quality of this chemical substance and suggest, but do not prove, a sensitization mechanism.

Tye⁸¹ reports a case of proven allergic contact-type dermatitis due to cigarette paper. Of course in this instance the localization of the eruption on the juxtaposed sides of the second and third fingers readily suggests a characteristic manipulation and makes investigation easy because attention is so strikingly directed. But considering the large number of objects the hands manipulate and the complex ways of manipulation, it can be imagined that it is not always easy to figure out what contacted where. For the discovery of contact allergens on the hands by those who do not themselves have extensive experience with such cases, the directions of Waldbott and Shea⁸² can be recommended.

Edelstein¹⁴ records an acute dermatitis apparently due to garlic. While it is not made clear whether the eruption was considered an allergic eczematous contact-type dermatitis, the positive patch test, which was read in five minutes because of intolerable burning at the site, suggests a primary irritant effect rather than a classical eczematous allergic reaction which has a reaction time of twenty-four to seventy-two hours. If the eruption was an allergic one it would be of interest to know whether it was due to a relatively small molecular fraction like an oleoresin or some characteristic protein in the garlic. We would suspect an oleoresin rather than a protein as the allergen cause.

Among the new chemicals that make for better living are the plastics. But to emphasize the drawbacks, Hirschmann²⁶ describes two cases of contact dermatitis

PROGRESS IN ALLERGY

from plastic tablecloths, and Templeton⁷⁶ records two cases proven by patch tests to be caused by plastic mittens. Jordan³⁴ reports cases of dermatitis from resins in shoe linings.

An interesting and practically important problem is what in plastics is the really culpable allergenic substance. High polymers themselves begin to pass out of the class of simple chemicals, if only in the sense of being substances of large molecular size. In general, it would seem that the larger the molecule, the less likelihood there is of eczematous sensitization, while urticarial and other types of allergenic states like the tuberculin type are readily caused by chemicals of large molecular size. It may be that the traces of simpler substances or less polymerized fractions in plastics are causative, and under some circumstances it may pay manufacturers to try to produce products less contaminated with such allergenic fractions.

ATOPIC DERMATITIS

Among the rarer and most dreaded expressions of atopic dermatitis is participation of the lens of the eye in the process. Thompson⁷⁷ re-emphasizes the problem of cataract formation in atopic dermatitis and lays out a dermatologic program of prophylaxis and of preoperative and postoperative care for cases of atopic dermatitis that come to ophthalmologic management of this condition. The rules and regimes devised by him seem reasonable, but whether they are efficacious—much as one may hope that they are—must be left for a longer and larger experience with such unfortunate cases.

L. Tuft, H. S. Tuft and Heck⁷⁹ are proponents of the view that inhalant allergens are important causes of clinical episodes of atopic dermatitis in adulthood. They cite such a case in which dermatitis could be reproduced regularly by controlled exposure to inhalant allergens, particularly house dust and *Alternaria*. There were positive skin reactions to house dust, *Alternaria*, and many food extracts; but only the inhalant allergens, not the foods, caused exacerbations upon deliberate exposure to the gross materials and upon intracutaneous injections of amounts that caused constitutional reactions.

Baagöe² considering the same point notes that it is only in those patients who have concurrent atopic expressions in the form of asthma and hay fever or other vasomotor rhinitis that the inhalants loom large as provocative factors of atopic dermatitis. Cases of atopic dermatitis that are not complicated by mucous membrane expressions of atopy do not seem to be affected by inhalant allergens.

The possibility that inhalant allergens are important in the production and maintenance of atopic dermatitis in adulthood is not new. It has long been noted that the ratio of positive skin reactions to foods and inhalants is reversed as the atopic patient passes from infancy into childhood, adolescence, and adulthood. Positive reactions to foods are present in greater proportion in the early years, whereas positive reactions to inhalants preponderate later. However, much as logic demands an explanation for clinical episodes of activity of atopic dermatitis, many things argue in the large majority of cases against the causal nature of allergens that are implicated by the skin testing. In most cases of hay fever and some cases of asthma, exposure to solitary allergens discoverable by skin testing regularly reproduces clinical manifestations, but the same thing is not a common finding in atopic dermatitis. Multiple positive urticarial skin tests are almost always the hallmark of the atopic state, but in our experience neither positive nor negative tests are a reliable therapeutic guide. In cutaneous atopy, it seems to us that the multiplicity of cutaneous urticarial sensitivities and their rapid waxing and waning as revealed by skin tests, coupled with seemingly unpredictable clinical remissions and exacerbations, make conclusions as to the etiologic significance of the allergens eliciting skin test reactions extremely difficult. The same difficulties are encountered to a lesser degree in tests of avoidance

PROGRESS IN ALLERGY

and re-exposure. It may be well to stress in this connection that in approximately one half of the cases which are *morphologically* diagnosed as atopic dermatitis, there is no evidence of an atopic state (no familial or personal history of other atopic diseases, no immediate wheal reaction in skin tests, no passive transfer antibodies in the blood serum, et cetera).

L. Tuft, H. S. Tuft and Heck⁸⁰ cite evidence suggesting that the sweat mechanism may be involved in atopic dermatitis in two ways. First, localized increased sweating in the affected areas *prior* to the outbreak of the lesions and, second, in the more severe and later stages plugging of the sweat ducts as had been previously described by Sulzberger, Herrmann and Zak.⁷² In the case described by Tuft et al the administration of Benadryl inhibited the localized sweating produced by inhalation of the specific allergen which suggests to them "the possibility that any beneficial effects obtained in atopic dermatitis patients from the antihistaminics might be due, perhaps even in large measure, to prevention of the inhalation of the specific allergen rather than a direct local effect on the skin." It appears to the reviewers that a much more acceptable interpretation might be the anticholinergic action of the antihistamines which, at least in some cases and to some degree, may inhibit the sweat impulses, which after all are mediated through the parasympathetic system.

These interesting studies again point up the fact how little we know about atopic dermatitis and that simple explanations such as "it's due to allergy" or "it's due to nerves" are unwarranted, incorrect, and unscientific even though they may sound like a satisfactory answer to the uncritical patient and, we are afraid, also the uncritical physician.

Cases of Kaposi's varicelliform eruption upon atopic dermatitis due to herpes simplex virus are reported by Brain, Dudgeon and Philpott,⁹ while Whittle, Lyell, Miles and Stoker⁸⁷ found vaccinia virus in their cases. These studies again point up the necessity that the nomenclature be made to conform to the virologic advances: the term Kaposi's varicelliform eruption should be dropped and the disease should be called "disseminated cutaneous herpes simplex superimposed on atopic dermatitis" or "disseminated vaccinia virus infection superimposed on atopic dermatitis" or whatever else the case may be. Aureomycin by mouth was found by Bookman⁸ to be effective in a case of Kaposi's varicelliform eruption presumably due to herpes simplex virus and by Perry and Martineau⁵² in a case of "eczema vaccinatum."

Rostenberg, Brunner and Riddell⁵⁸ observed no antipruritic effect from My-B-Den (adenosine-5-monophosphate) in atopic dermatitis. This is not surprising, since this preparation appears to be generally useless against itching, with the possible exception of the itching associated with the varicose symptom complex.

DRUG ERUPTIONS

The variety and ubiquity of drug eruptions never ceases to amaze. Hardly a substance remains exempt from suspicion of being capable of inducing an eruption that is unrelated to its expected pharmacologic action as a drug.

Nelson⁴⁶ and Reiche⁵⁵ each reported a case of dermatitis medicamentosa from undecylenic acid. As though it is not bad enough that undecylenic acid is useless for its recommended purpose, it further shows itself to be capable of doing positive harm (severe generalized eruptions) instead of just nothing for psoriasis.

Sweet⁷⁵ reports a fixed eruption from phenytoin sodium consisting of bullae and plum-colored macules. Classical descriptions of fixed eruptions stress recurrence in an original site of eruption and erythematous to purplish plaque-like lesions as the usual morphologic forms. Fixed urticarial eruptions and of late many instances of vesicular and bullous fixed eruptions also have been described. Tolmach and Frank⁷⁸ have seen a case of a vesicular and bullous fixed eruption from bromides. The sole distinguishing characteristic of a fixed drug eruption then is that startling recurrence in the same site and not necessarily the morphe of the clinical lesion.

PROGRESS IN ALLERGY

In this connection a report of a fixed drug eruption from Antabuse by Lewis and Bremers³⁸ deserves note. They saw a recurrent eruption consisting of erythema and excoriations (owing to pruritus, apparently) of the gluteal, inguinal, scrotal, lower abdominal, axillary and cervical regions following regularly upon the administration of tetraethylthiuram disulphide (Antabuse) and alcohol. It is noted that pharmacologically a characteristic effect of this drug consists of intense erythema of the face, neck, upper chest and arms, accompanied by injection of the sclera. Acetaldehyde is increased in the blood as a result of Antabuse exhibition followed by alcohol and is thought to be responsible for the disagreeable effect that makes Antabuse useful for the treatment of dysomania. The eruption described, which is considered a fixed drug eruption, sounds much like the pharmacologically characteristic one except for its location and the pruritus that attended it.

Reports of eruptions from antibiotics continue to appear in fair volume and are attended by admonitions about indiscriminate use of these valuable agents in conditions where there is no reason to use them nor reasonable hope that they will be effective. Despite such repeated warnings, the antibiotics are probably prescribed with the old abandon, or if there has been less general and more discriminating prescription, it probably has been more on account of expense of the newer antibiotics and the troublesome injection methods necessary for the administration of the older ones.

It is well, however, to realize that when reactions occur after the administration of antibiotics the reactions can have been caused by other materials in the preparations. For example, lozenges and troches contain excipients and dyes that may cause eruptions; injectables contain local anesthetics, preservatives, oils, waxes, or other agents designed to retard the absorption of the antibiotic that may give trouble without the antibiotic being at fault. Examples of this circumstance are the reports of Kile³⁶ and of Hitschmann, Leider and Baer²⁷ where sensitization was traced to the procaine fraction of procaine penicillin rather than the penicillin itself, an occurrence which had been previously described by Peck and Feldman.⁵⁰ It is obviously important to know of the possibilities of such occurrences in order to be able to administer potentially life-saving treatment with penicillin—simply with the variation of using a preparation without procaine. In line with this is a report by Samitz, Horvath and Bellet⁵⁹ of a hemorrhagic bullous eruption that was elicited by penicillin G but not by penicillin O. Another approach to the problem of cutaneous penicillin hypersensitivity is the so-called "hypoallergenic penicillin" which actually is a mixture of an antihistaminic drug with injectable penicillin. This combination is reported to be less sensitizing, according to Simon and Feldman.⁶⁴

The amazing therapeutic efficacy of the antibiotics is matched in a way by the multiplicity and variety of reactions to them. Aside from the nonallergic effects like nausea from aureomycin, vestibular disturbances from streptomycin, anal pruritus from aureomycin, et cetera, there are well-known reactions based on acquired sensitization.

When it comes to eruptions in the mouth, it is frequently difficult to tell whether the reaction is of allergic or nonallergic mechanism. Goldman and Tronstein²¹ investigating mucous membrane sensitization found that sometimes positive patch test reactions on the mucous membrane developed in agreement with positive cutaneous patch tests, but not inevitably so. They conclude that there is greater ease in acquiring allergic eczematous contact-type *dermatitis* than contact-type *stomatitis*. This is not to say that stomatitis in itself is not common from antibiotics that are administered in the form of troches. A high incidence of positive oral mucous membrane contact tests among patients with allergic contact dermatitis was found also by Bisgaard Lefevre.⁶ Fisher and Leider¹⁵ designate a type of stomatitis as "aureomycin or penicillin mouth" and list the possible causes as (1) an imbalance in the floral pattern caused by the antibiotics, resulting in moniliasis,

PROGRESS IN ALLERGY

(2) an avitaminosis (ariboflavinosis) caused by disturbance in production or utilization of some fraction of the vitamin B complex, and (3) a sensitization to the antibiotic or some other agent in the troche. In their cases of aphthous stomatitis, ariboflavinosis seemed to be the commonest cause of stomatitis that occurred as a complication in the course of treatment.

It is well known that streptomycin is a powerful eczematogenic sensitizer. Sulzberger and Distelheim⁷¹ report a case in which dihydrostreptomycin evoked allergic eczematous contact-type sensitivity of equal degree with that of plain streptomycin.

An interesting case of a vesicular eruption in an eleven-day-old infant due to bromides ingested by the mother is reported by Yeung.⁸⁸ The mother herself did not have an eruption.

For allergic reactions to the antihistaminic drugs see below under "Antihistamines."

URTICARIA

Urticaria remains an exasperating therapeutic problem despite the help from the so-called antihistamines. Discovery and elimination of cause is still the often difficult but the only definitive solution.

Blank and associates⁷ made a contribution to such definitive solution of papular urticaria by tracing many of their cases to insect bites. They noted the well-known similarity of appearance between many cases that are designated as papular urticaria and insect bites. Aside from the clinical similarity the appearance of the condition in the warm season and in groups of lower social and economic levels, disappearance of the condition upon hospitalization, and a high rate of positive reactions to extracts from fleas and bedbugs are submitted as additional evidence of causation by insects. Finally, treatment of the patients' surroundings with DDT proved efficacious in 86 per cent within two weeks, whereas in a control group treated by other modes only 21 per cent were benefited. Of course it has been known for many decades that there can be a close resemblance between insect bite eruptions and papular urticaria. Nevertheless, there are cases of papular urticaria which are a variety of atopic dermatitis. The importance of the work by Blank et al is that it seems to show the high incidence of cases considered atopic which are nothing more than cases of zoonoses that are mislabeled and, thus mislabeled, bear a less happy prognosis than does a dermatosis caused by a biting parasite.

Cohen and Criepe¹⁰ found *Endameba histolytica* in nineteen cases of urticaria and/or angioneurotic edema. Upon adequate emetine therapy, resulting in eradication of the parasite, the whealing episodes ceased. This effect after long duration of the condition speaks for causal relation between the infestation and the urticaria.

Herlitz²⁵ described two cases of urticaria following physical exertion and implicated lactic acid as the causative allergen. Hyposensitization by injection of graded amounts of lactic acid is said to have been achieved and to have produced a beneficial therapeutic result. Marcussen⁴¹ described a syndrome which he calls dermographic prurigo-like lesions in areas of friction.

Sherman and Seeborn⁶³ report an excellently studied patient with cold urticaria whose sensitivity could be passively transferred with the blood serum. The skin sensitizing activity of the serum was only slightly affected by heating for one-half hour at 56° C. but was destroyed by heating for four hours at this temperature. Attempts were unsuccessful to demonstrate reversed passive transfer and to isolate an antigen liberated from normal skin by cold which would react with the serum. The following four fractions were separated from the patient's serum: (1) albumin, (2) albumin and alpha globulin, (3) beta and gamma globulin, and (4) gamma globulin. These fractions singly did not sensitize normal skin, but mixtures of all four fractions or of the second and third fraction did sensitize normal skin. This suggested to Sherman and Seeborn that the presence of more than one protein

PROGRESS IN ALLERGY

component was necessary to produce sensitization. Another case of urticaria due to cold but without demonstrable passive transfer antibodies is cited by Rajka and Asboth.⁵⁴

THE ANTIHISTAMINES

The word "antihistamine" is probably by now so well established that no amount of argument about its uncertain propriety will avail. That it assumes a mechanism of medication of allergic manifestation through histamine which even in the urticarial reactions is not entirely proven, that it suggests that the clinical effects are based on chemical antagonism to histamine which is more unproven, that the agents so designated have very marked other effects like sedation, local anesthesia, hyaluronidase-inhibitory and anticholinergic actions which are quite potent—all such considerations cannot budge the generic descriptive word "antihistamine." As it is, a generation of physicians is growing up with the concept that histamine and allergy are irrevocably married. It can be hoped that the limitations and circumscribed effectiveness of the antihistamines will eventually shake confidence in this largely unwarranted connection.

Perhaps the most interesting report dealing with antihistamines during the past year is that of Monash.⁴³ He demonstrated in several subjects that, once an adequate single dose of an antihistamine has been administered, there develops in many persons a tolerance to the effects of the drug as far as its capacity to inhibit histamine whealing is concerned. Thus the same dose of an antihistamine which after its first administration may be capable of depressing a given patient's histamine whealing threshold from 1:3,000,000 to 1:100,000 may several days later be capable of lowering the threshold only from 1:2,000,000 to 1:1,000,000. If Monash's finding is confirmed, it will explain many of the clinical observations regarding loss of efficacy of antihistamines which hitherto have been unexplained. Moreover, it will be another piece of evidence against the theory that the clinical efficacy of antihistamine is based on their "antihistaminic" action. It must, however, be remembered that Monash's observations bring no evidence that there is a tolerance also regarding the other important effects of antihistamines such as local anesthetic action, hyaluronidase-inhibiting action, anticholinergic action, "central" action including antimotion sickness effect, et cetera.

Several reports have now been added to the previous ones of urticaria and allergic eczematous dermatitis from the antihistamines. Pratt⁵³ reports a case from each of these categories. One lesson that cannot be avoided from these cases is that any simple chemical must be suspected of capacity to engender allergic states, even those that are designed to counteract allergic states. Another lesson is this paradox noted in the articles by Pratt⁵³ and Warin⁵⁴: How can the antihistamines be antihistaminic if they provoke histamine effect and then fail to suppress histamine effect? It seems to the reviewers that this is at least partially a semantic paradox.

Waldriff et al⁵⁵ review the theory of histamine mediation of allergic states and the pharmacologic history of the development of so-called antihistaminic agents and then evaluate the therapeutic effectiveness of seven of these agents and their side effects. In brief, cases of urticaria are said to be benefited to an extent of 80 per cent of all cases; localized and disseminated "neurodermatitis" improved 50 per cent of times; the pruritus of contact dermatitis and of the anogenital region were also relieved in variable high percentage. Side reactions occurred in 70 per cent of cases; eczematous sensitization occurred 5 per cent of the time from topical application. The discussion published with Waldriff's paper records the experiences of various observers both as to clinical effectiveness and side effects of these drugs. One is left with the impression that while there is an over-all judgment of usefulness for this class of agents, there is an undertone of vitiation of their usefulness by the volume of undesirable side reactions, particularly allergic reactions.

PROGRESS IN ALLERGY

Sherman and Cooke report cases of contact dermatitis due to Pyribenzamine and Antistine, Mosko and Peterson⁴⁵ a case due to Antistine.

Dale, who has had so much to do with studies in histamine, reviews¹³ the theory of action of histamine and notes the general similarity in molecular structure between histamine and many of the antihistamines. He suggests that the mode of action of the so-called antihistamines is by attachment at the cell surface where histamine might ordinarily attach and cause its characteristic effects. This is reminiscent of the theory of action of the sulfonamides, which are antibacterial by virtue of being taken up unwittingly by pathogens instead of paraaminobenzoic acid which is nutrient to them. Apparently bacteria, being unable to metabolize sulfonamides, then starve to death. If Dale's account is correct, then the antihistamines are not so much antihistaminic as parahistaminic, i.e., much like histamine, being attachable to cells but different in effect after such attachment. As to clinical result, in urticaria, where evidence of histamine mediation is strongest, it may be expected that the antihistamines will be most effective, which is indeed the case. But pruritus of origin or mechanism other than urticarial may not be expected to be relieved, unless it be due to the sedative and local anesthetic action of these drugs. Dale ends his paper with a suggestion for a pretty experiment which would tell something more of the pharmacologic and physiologic action of the antihistamines. Recalling that parenteral administration of histamine provokes a rise in gastric hydrochloric acid, he asks what would be the response to antihistamines? To this one can comment that experiments by Haljern, Hamburger and Debray²³ have shown that the administration of antihistamines does *not* interfere with the hydrochloric acid secretion-stimulating action of histamine; for some animals who are given antihistamines to prevent histamine shock die of perforated gastric ulcer although they survive the histamine shock.

Peck et al,⁵¹ studying the effects of Pyribenzamine on the histamine wheal and on sensitivity reactions, come to many interesting conclusions: namely, (1) that both the mode of administration and amount of Pyribenzamine determine the effects of this drug, (2) that oral, local, parenteral, and iontophoretic exhibition reduce the histamine wheal and flare, (3) that reactions of epidermal sensitivity as exemplified by patch tests are not influenced by oral or local parenteral administration but that previous iontophoresis of Pyribenzamine reduces the patch test reaction whereas novocaine thus introduced is ineffective, (4) that Pyribenzamine cannot be detected in the urine when inunction into normal skin but can be demonstrated in the urine when applied over areas of dermatitis, (5) that it can be demonstrated in appreciable amounts after iontophoresis into normal skin, and (6) that iontophoresis of Pyribenzamine seems to have a prophylactic and protective effect against established epidermal sensitization.

MISCELLANY

In the recent literature short notes have appeared by Morgan⁴⁴ and Bardach,⁵ both of which deal with a "suggestive sign of allergy." The subject involves a certain puffy appearance of the lower lids that is said to be characteristic of "allergy." We are not concerned so much with the verity of the sign as with the phrase "sign of allergy." The most superficial examination of articles that use the words "allergics," "allergic history," or "allergic background" reveals that what is in mind is that *one* category of allergy that has been designated by Coca as atopy. It has been stressed repeatedly that narrowing the meaning of the word *allergy* to synonymity with *atopy* creates a confusion in the study of allergic phenomena. As a result, allergic states that have nothing to do with genetic factors have such extraneity dragged in by the heels by needless references to "allergic history." Allergic states of eczematous character, most drug eruptions based on allergic

PROGRESS IN ALLERGY

mechanism, and most of allergy of infection have nothing to do with a predisposition to develop allergic states and still are as properly designated allergic as any atopic state. There is no reason why one should not continue to designate by *atopy* those allergic states that are based on a certain type of inborn diathesis and never to vitiate the general character of the word *allergy* by using it in equality with *atopy*. Truth to tell, the only suggestive sign of allergy is the quality of being alive. Everybody has the capacity to develop allergic states of some sort and indeed everybody does. Some human beings are capable of developing both atopic and nonatopic allergic states, although more human beings are capable of developing only nonatopic allergic states.

It is appropriate to all of the preceding substance to close this review with reference to the Prosser White Oration delivered in London last year by Sulzberger under the title "Allergy: A Dermatologist's Reminiscences and Speculations."⁶⁸ All who are interested in the historical development of the subject of dermatologic allergy will be rewarded by a close reading of this paper by one who has been so pre-eminent in advancing this particular field to its present high level.⁷⁴ For here in characteristically clear, concise, and instructive style, Sulzberger presents what is in the reviewers opinion the best summary of the basic concepts and methodology of allergy. In its wider implications, the work covered in this excellent paper constitutes one of the significant advances in medicine in recent years.

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THE EDITOR'S PAGE

(Continued from Page 398)

of larger doses of ephedrine with adjuvants for the control of side reactions might lead to some reportable results in the emphysematous asthmatic groups of patients.

If this feature of an editor's page remarking on papers which point the way to future studies in the field of allergy meets with favor, it will be continued now and then, by one or another of the Editors.

—E.A.B.

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News Items

EIGHTH ANNUAL CONGRESS

All members of the College are cordially invited and urged to attend the Eighth Annual Congress of The American College of Allergists, April 7, 8, and 9, 1952, which will be preceded by a three-day Instructional Course, April 4, 5, and 6, at the Hotel William Penn, Pittsburgh, Pennsylvania. You will be assured of satisfactory accommodations at the headquarters hotel, and an elaborate plan for entertainment is now being prepared for all the members and their families.

Cordially yours,

THE LOCAL COMMITTEE

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INFORMATION REQUESTED

Prof. Piero Sangiorgi, M.D., Secretary of the Italian Association for the Study of Allergy, will discuss "Geographical Distribution of Diseases Due to Allergies" at the First International Congress of Allergists to be held at Zurich, Switzerland, September 23-29, 1951.

Prof. Sangiorgi asks all of the colleagues of every part of the world to send to him all the information which may help him complete this work: that is, statistical data, regional clinic observations, publications, et cetera. The names of the authors will be mentioned in the final report.

Write to Prof. Piero Sangiorgi, M.D., Via Rivoli 2, Milan, Italy.

MEXICAN SOCIETY OF ALLERGISTS

The Fifth Annual National Convention of the Mexican Society of Allergists, together with an intensive course on allergic diseases, was held February 19-24, 1951, in the city of Morelia, under the auspices of the Society of Allergists and the University. Chairman of the course was Dr. Mario Salazar Mallen; Secretary, Dr. Julio Cueva.

Those who participated were Drs. Arturo Blackaller, Jose Luis Cortes, Oscar de la Fuente, Rafael de la Parra, Manuel Medina, Emma Rodriguez Herrera, Jose Sanchez Cortes, Fernando Velarde Thome, Juan Manuel Lopez Sanabria, Oscar

NEWS ITEMS

Lozano, J. U. de la Vega, Hector Davalos, and F. Martinez Cortes. The course embraced basic concepts of allergy, with clinical and theoretical procedures, and the etiology and management of various allergic diseases.

CUBAN SOCIETY OF ALLERGY

New officers for the Cuban Society of Allergy have just been announced. The governing body for 1951 is as follows:

President: Dr. Jose M. Quintero Fossas

Vice President: Dr. Julio de los Santos

Secretary: Dr. Gonzalo Estrada de la Riva

Treasurer: Dr. Jose Pedrera Rodriquez.

Board: Dr. Jose Cadrecha Alvarez, Dr. Josefina Amiguet Villagrasa, Dr. Javier Fernandez de Castro.

ACA MEMBER HONORED

Friends of Morris Scherago, D.V.M., will be pleased to learn that he has received the honor of "Distinguished Professor of the Year" at the University of Kentucky. His lecture was entitled "The Biological Basis of Allergic Reactions." The honored professor customarily is granted a term free from teaching duties in order that he may give full time to some research project and prepare the annual Arts and Sciences lecture. Doctor Scherago plans to leave June 1 to teach and study tropical diseases in Siam, and will be away for at least a year. The College extends heartiest congratulations.

CLINICAL NOTES

The extraordinary increase in the medicinal requirements for cortisone has far outstripped present production capacity. The present shortage of cortisone is due to shortage of supply of starting material: cattle bile. Intensive research is being undertaken by Merck & Co., Inc., to improve current processes, to find new and more abundant starting materials for cortisone manufacture, and to discover a key to complete chemical synthesis. Cortisone is now made by four licensed firms.

Merck & Co. has made six price reductions in the price of Cortone† since August, 1949, when the first limited quantities were offered for clinical investigation at a price of \$200 per gram. The present price to wholesalers is \$22.40, almost 90 per cent below the original figure. Merck's suggested price to pharmacies and hospitals is now \$28 per gram, and to physicians \$35 per gram.

* * *

The Hypospray jet injector—an instrument for giving subcutaneous and intramuscular injections without a needle—has just been introduced by the Scherer Corporation, Parenteral Products Division, 9425 Grinnell Ave., Detroit 13, Michigan. Controlled pressure provided by the spring-activated plunger of the Hypospray causes a fine jet of medication to penetrate to the desired depth with little or no pain. Satisfactory clinical evaluation has been accomplished. It is expected that the Hypo-spray will be available to physicians nationally in about a year.

†Registered trade name.

BOOK REVIEWS

STRESS. By Hans Selye, M.D., University of Montreal. 822 pages, 203 pages of references, numerous figures. Price \$14.00. Montreal, Canada: Acta, Inc., 1950.

This is a tome by the maestro.

All scientists interested in the general-adaptation-syndrome and allied phenomena of the author have undoubtedly read some of the reviews reflecting different points of view which have appeared in English and twelve other languages.

Since adaptability is one of the most distinctive characteristics of man, the forces which cause normal adaptation are of vital interest to physiologists, pathologists, biochemists, endocrinologists, hematologists, and specialists who confine their studies to the various domains of the body. The author has very successfully integrated a vast number of observations which clarify our knowledge of heretofore puzzling syndromes with one common denominator. According to our present knowledge, however, a large group of human diseases cannot be explained as the result of or associated with chronic stress situations but may be as the result of altered or abnormal adrenal-cortico function.

Besides a comprehensive table of contents, there are a historical sketch, a text of 817 pages including an index, and 5500 references which are exhaustive in their scope. To give an idea of the range of this book, an enumeration of some of the sections is presented: both general and special physiology and pathology of systemic stress; metabolism; hormones and hormone-like substances, as well as enzymes; vitamins; all the present knowledge on the endocrines; the skeletal system; blood count, including blood diseases of adaptation; the hemopoietic system; the cardiovascular, respiratory, muscular, nervous, and gastrointestinal systems; the liver, kidney, skin, and appendages; and serologic reactions. About all of these subjects, facts and theories concerning their particular place in the general-adaptation-syndrome are integrated.

There are numerous figures including excellent photographs, both microscopic and gross, and diagrams explaining the author's concepts. The binding is durable; the print is very clear and readable on a pure white, heavy paper stock. Every physician, whether specialist, general practitioner, or student of medicine or its allied sciences, should include this volume as one of his main references.

FOOD ALLERGY. By Herbert J. Rinkel, M.D.; Theron G. Randolph, M.D.; and Michael Zeller, M.D. Price \$8.50. 497 pages, 25 illustrations, 182 recipes. Springfield, Ill.: Charles C Thomas, 1950.

This book is an exposition of the dynamic nature of food allergy and presents for the first time the minute clinical details of food sensitivity. The authors consider food allergy as fixed, cyclic, or intermittent, the latter being the most frequent. Methods of testing and basic diets are emphasized in detail. The reader's attention is directed to the fact that reference to sensitizations of "food allergy" have been proven at will, and mixed sensitizations such as inhalants have been evaluated and controlled so as not to confuse interpretation of a reaction. In other words, when the authors say "a series of 200 food allergy people," they mean 200 patients in whom sensitization of food is proven beyond any reasonable doubt.

The authors also point out that all fractions of a food should be eliminated until the patient is freed of symptoms before determining whether the oil or sugar or

BOOK REVIEWS

starch of such a food will produce clinical symptoms. The basis for this work is represented in the deliberate individual food tests of more than 50,000 observations and has not been compiled from questionnaires. This book is adequately illustrated and contains the highlights of the details of the Food, Drug and Cosmetic Act.

PRACTICE OF MEDICINE (FIFTH EDITION). By Jonathan C. Meakins, M.D., formerly Professor of Medicine and Director of the Department of Medicine, McGill University; formerly Physician-in-Chief, Royal Victoria Hospital, Montreal; and formerly Professor of Therapeutics and Clinical Medicine, University of Edinburgh. 1558 pages, 518 illustrations, including 50 in color. Price \$13.50. St. Louis: C. V. Mosby Company, 1950.

This tome is encyclopaedic in scope, being written for the general practitioner. The author appreciates the difficulties of writing a new edition, because of the increasing flood of specialized techniques. He has succeeded admirably in organizing diagnostic and management procedures of practical value without neglecting essentials. Modern protective immunization measures and chemotherapy are harmonized with functional disturbances based upon pathophysiology.

All the chapters have been brought up to date. The chapter on endocrine glands has been largely rewritten, and a basic chapter on allergy is included. There are twenty-three chapters covering adequately every phase of medicine. As is usual with Mosby publications, the binding, printing, and styling are very good. Osler would be pleased with this edition.

Just Off the Press—

ALLERGY IN RELATION TO PEDIATRICS

representing the Panel on Pediatrics, April 17, 1949, Chicago

An Official Publication of The American College of Allergists, Inc.
in co-operation with The American Academy of Pediatrics

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